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THE METABOLISM AND UTILIZATION OF PROGESTERONE GIVEN INTRAMUSCULARLY TO WOMEN*

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GYNECOLOGISTS long have felt the need for an active therapeutic agent having the specific endocrine properties attributed to the corpus luteum. Now that synthetic progesterone has been available for approximately four years, it seems advisable to examine certain clinical data which are pertinent to its pharmacology.

PRELIMINARY CONSIDERATIONS

The early aqueous extracts of corpora lutea had no demonstrable potency. Iscovesco[1] in 1914, however, prepared a lipoid extract which he used clinically with some apparent success. Hermann[2] in 1915 probably produced experimentally progestational alterations of the endometrium with one of these lipoid extracts, but it is believed generally that he did not recognize these changes. Hisaw and his group[3] in 1928 prepared extracts which definitely contained the active principle of the corpus luteum. The same year Corner[4] confirmed the observations previously made in 1910 by Ancel and Bouin[5] that the characteristic progestational reaction of the uterus of the gravid rabbit was due to the specific action of the corpus luteum. Corner and Allen[6] in 1929, employing a modification of Hermann's technique of extraction, were able to prepare an alcoholic extract of corpora lutea of sows which was capable of inducing a progestational reaction in the

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endometrium of the castrated rabbit. This reaction came to be adopted generally as a method of bio-assay for the active principle of the corpus luteum (Corner-Allen rabbit unit).

Despite these significant studies, the pharmaceutical chemists encountered difficulties in preparing an active extract for clinical use due to the low yield of progestin by corpora lutea of various animals. Moderate amounts were found in the corpora lutea of hogs and cattle, but only small amounts occurred in those of the sheep. Pratt, Hamblen, Kamm and McGinty[7] reported also that the corpora lutea of women contained quite small amounts of progestin: they found that an equivalent of 60 to 100 gm. of fresh corpora lutea was necessary for a positive reaction in the immature rabbit. They observed: ''A pair of mature hog ovaries contains in the order of magnitude 20 to 30 times as much progestin as the human ovary. According to the determinations, it takes nearly 40 human corpora lutea to yield 1 Rb. U. of progestin.'' Various possible explanations of these findings were suggested: the low content of progestin in the human being might indicate a greater sensitivity, with the result that a small amount of the hormone is relatively more effective; on the other hand, progestin might not be stored long in the corpus luteum, but rather might be secreted into the circulation as soon as elaborated. The failure, however, of Bloch[8] to find any progestin in 500 c.c. of blood from a pregnant woman, and the inability of Loewe and Voss[9] to detect but small amounts in pooled specimens of urine from women during the progestational phase of the menstrual cycle were opposed to the latter assumption.

Attempts to circumvent the lack of active preparations of progestin by giving gonadotropic substances derived from the urine of pregnancy were unsuccessful. The theoretical basis for this form of therapy was the assumption that these ''luteinizing principles'' might cause the ovaries of patients in need of progestational effects to form functional corpora lutea and thereby to form their own progestin. Studies at our clinic[10] during the past ten years have convinced us that even the present preparations of gonadotropes will not produce ovulation and the formation of corpora lutea in ovaries not spontaneously capable of performing these functions. There is a possibility, however, that in certain patients whose corpora lutea are functioning at low levels these may be caused to elaborate more progestin by treatment of this sort.

A practical commercial method for the preparation of quantities of the progestational principle adequate for clinical purposes was made possible by the synthesis of progesterone.

Almost simultaneously in 1934 three groups of workers, Butenandt, Westphal and Cobler,[11] Slotta, Ruschig and Blanke,[12] and Allen and Wintersteiner,[13] isolated crystalline progesterone. The same year Butenandt and Westphal[14] synthesized it from stigmasterol, and later Butenandt[15] announced its preparation from pregnandiol.

There seems to be general agreement among experimental workers that synthetic progesterone possesses all the pharmacologic properties exhibited by active extracts of corpora lutea.

Corner and Allen,[16] upon the basis of observations by them and their group[17] upon laboratory animals, drew the following conclusions: ''It may be stated that all 4 of the definitely established effects of corpus luteum extracts upon the uterus; namely, progestational proliferation of the endometrium, inhibition of the

action of pituitrin upon the myometrium, inhibition of uterine motility in vivo, and the suppression of menstruation have now been achieved with crystalline progesterone.''

The foregoing conclusions, unfortunately, have not been proved for woman. For the most part critical clinical studies have been concerned with investigations of the endometrial responses, as judged from specimens obtained by curettage or biopsy.

Clauberg[18] in 1932 and Kaufmann[19] in 1933 reported that progestational reactions had been produced in the endometria of castrates by the employment of estrogens and of extracts containing progestin. The doses employed by these two workers were similar: Kaufmann, for example, used a total of 42,000 R.U. of estradiol benzoate given over a period of twenty-one days and followed by a total of 35 Rb. U. (Clauberg units) of progestin given over an interval of seven days. Elden,[20] however, repeated the work of Kaufmann and Clauberg. He was unable to produce progestational alterations in the endometria of 5 human castrates by series of injections of estradiol benzoate, averaging 50,000 R.U. given over periods of fifteen days, which were followed by those of progesterone in amounts ranging from 12 to 60 Rb. U. (Corner-Allen units, each of which is usually considered to be equivalent to 2 or 3 Clauberg units) spread over intervals varying from one to six days. Observations similar to those of Elden, but made upon young women with menometrorrhagia associated with estrogenic endometria rather than upon castrates, were reported about the same time from our clinic.[21] It was observed that injections of progesterone, alone or of estrogens and progesterone together, given similarly to those of Clauberg, Kaufmann and Elden, failed to produce any significant endometrial alterations similar to those occurring during the progestational phase of normal cycles. In a few instances, however, mixed endometria (those with localized or patchy areas of progestational reaction) were encountered after combined therapy with estrogens and progesterone.

The important studies of Venning and Browne[22] in 1936 and 1937 permitted an approach to the clinical investigation of the pharmacology of progesterone which was quite different from those aimed at detecting endometriotropic responses. Venning[23] described a gravimetric method for the quantitation of sodium pregnandiol glucuronide in the urine. She and Browne shortly thereafter submitted evidence that this pregnandiol-complex represented an end-product of the metabolism of progesterone.

All previous studies designed to identify progestin in blood or urine by methods of bio-assay had been singularly unsuccessful. Studies in our clinic[24] have confirmed the fact that the pregnandiol-complex represents an end-product of the metabolism of progesterone. We called attention, however, to limitations necessary in the interpretation of data secured by this method. Our observations were summarized as follows:

(1) Four factors are concerned in the metabolism of progesterone and in the subsequent urinary excretion of sodium pregnandiol glucuronide: (a) *ovarian,* involving the formation or progesterone by post-ovulational corpora lutea and possibly from the marginal granulosa luteinization of follicles; (b) *endometrial,* concerned with the alteration of progesterone into pregnandiol; (c) *hepatic,* which brings about the conjugation of pregnandiol with glucuronic acid; and (d) *renal,* involving the excretion of sodium pregnandiol glucuronide. (2) The excretion of this compound indicates the functional capacity of all these factors; the absence of the compound from the urine indicates the functional failure of one or more of

the factors. (3) A failure of excretion is not conclusive evidence that ovarian function is inadequate. (4) The excretion of the pregnandiol-complex is not evidence that an endometrium is undergoing progestational proliferation.

THE CLINICAL APPROACH

The factual data to be considered in the present report were secured during the course of the diagnosis and treatment of a group of patients with diverse functional irregularities of uterine bleeding. These data will be segregated into two groups: (1) those concerned with evaluation of the endometriotropic effects of progesterone injected intramuscularly, these effects being judged from the study of serial endometrial specimens secured by biopsy (evidences of endometrial utilization); and (2) those dealing with evidences of metabolic alterations of the progesterone injected, these being based upon determinations of urinary titers of sodium pregnandiol glucuronide.

All of these patients received, during the period of observation to be reported, a system of cyclic therapy either with progesterone alone or with estrogens and progesterone combined. The details of this method of treatment have been reported previously by one of us.[25] They will be summarized briefly at this point:

If menorrhagia or metrorrhagia existed, a remission from bleeding was induced, if necessary, by estrogenic therapy or by a thorough curettage. One week after curettage or directly following the cessation of an episode of bleeding, injections of estrogenic substance in daily doses of 10,000 to 20,000 international units were begun and continued for fourteen days. Progesterone in daily doses of 5 to 10 international units was then started and given daily for seven days. In some instances, daily injections of 10,000 international units of estrogens were continued during the time that progesterone was administered. At the conclusion of this treatment, and frequently before all the progesterone had been given, bleeding occurred. This bleeding has been found, as a rule, to be comparable in amount and duration to that experienced by healthy women. No treatments were given during the week set aside for bleeding. Injections of progesterone were discontinued if bleeding started early. One week after the onset of bleeding, treatments were repeated in the same manner. If bleeding still persisted, the injections of estrogens were found to cause it to cease. Some patients were given only progesterone cyclically. This treatment differed from that described only in the fact that no estrogens were employed; the temporal relationship between treatments with progesterone and bleeding remained the same.

During the period of treatment, endometriotropic effects were judged by biopsies of the endometrium taken at the onset of bleeding, but no later than twelve to twenty-four hours from that time, since the processes of tissue-shedding, necrosis and subsequent regeneration confuse the interpretation of tissue secured later in the course of flowing.

In the group of patients, whose urinary titers of sodium pregnandiol glucuronide were investigated, the following routine was followed. The method of quantitation employed was that described by Venning.[23] Twenty-four-hour specimens of urine were used. No specimens were taken during episodes of bleeding. As a rule daily urines were required during the period of injection of both estrogens and progesterone. In some instances specimens were secured only during the time when progesterone was given. Unfortunately, in some instances, cooperation of the patient was not ideal and specimens were missing at times when their contents might have proved significant. In reporting the values obtained from these studies, we have followed the practice of Venning and given the total

amount calculated to be present rather than the amount actually extracted (i.e., added a correction for the percentage of a known amount not extractible by the method employed).

ENDOMETRIOTROPIC DATA

These data were obtained during the course of 117 series of cyclic therapy with ovarian sterols given 23 women with functional irregularities of uterine bleeding. All preparations of these sterols were employed in solutions of oil and were given intramuscularly. The ages of these women varied from 12 to 37 years, the majority being under 25 years of age.

The endometrial findings are designated by the following symbols, according to a system of classification[25, 26] employed in our clinic:

E- hypoestrogenic or atrophic endometrium.
E persistent estrogenic endometrium.
E+ hyperestrogenic or hyperplastic endometrium.
M mixed or irregularly ripened endometrium.
P progestational endometrium.
These clinical data are presented in Table I.

Each patient received an average of approximately 5 cycles of therapy. The greatest number of cycles was 9; each of 2 patients received this number. The smallest number of cycles of therapy was 1; this was given only 1 patient.

The 117 cycles of therapy were distributed as to kind as follows:

Estrogens* followed by progesterone (e - p)   46 cycles
Estrogens followed by estrogens and progesterone   21 cycles
   (e - e + p)
Estrogens and progesterone (e + p)   9 cycles
Progesterone alone (p)   41 cycles

   Total   117 cycles

The total doses of progesterone given during the 117 cycles varied from 5 to 65 mg. The frequency of the different doses was as follows:

5 mg.   2 cycles   20 mg.   4 cycles
10 mg.   8 cycles   25 mg.   6 cycles
15 mg.   4 cycles   30 mg.   7 cycles
                          35 mg.   47 cycles

40 mg.   12 cycles   60 mg.   1 cycle
45 mg.   9 cycles   65 mg.   1 cycle
50 mg.   16 cycles

The total amount of progesterone given was 4,045 mg. The average dose for a cycle of therapy was 34.5 mg.

A total of 129 endometrial specimens was studied: 23 before treatment; 99 during therapy; and 7 after the discontinuation of therapy.

Before therapy the endometrial findings were distributed as follows:

E (persistent estrogenic)   13 patients
E+ (hyperestrogenic)   6 patients
M (mixed)   4 patients

   Total   23 patients

*The estrogens employed in these studies were estrone and estradiol benzoate.

TABLE I. DATA REGARDING ENDOMETRIOTROPIC RESPONSES TO CYCLIC THERAPY WITH PROGESTERONE

PATIENT	CYCLES OF THERAPY	ENDOMETRIAL FINDINGS AND ANTECEDENT THERAPY*		
		BEFORE TREAT-MENT	DURING TREATMENT	AFTER TREAT-MENT
Case 1	4	E	E 35 (e – p); E 35 (e – p); E–35 (e – p); E– 50 (p)	E–
Case 2	9	E	E– 35 (e – p); M ? 35 (e – p); O 35 (p); M ? 25 (e – p); E 10 (e – p); E 50 (e – e + p); E 50 (e – e + p); E 45 (e – e + p); E 50 (e + p)	O
Case 3	8	M	E 10 (e – p); E 10 (e – p); E 5 (e – p); E 45 (p); M 45 (p); E 25 (p) E 25 (p); O 40 (e – e + p)	E
Case 4	6	E	E 35 (e – p); E+ 35 (e – p); E 35 (e – p); E 40 (p); E 50 (p); E 50 (p)	O
Case 5	1	E+	E 35 (e – e + p)	O
Case 6	7	M	E 40 (p); E 35 (e – e + p); E– 35 (e – p); E 35 (e – e + p); O 35 (e – e + p); E 35 (e – p); E 35 (e – p)	O
Case 7	9	E	O 15 (e – p); E 10 (e – p); E 5 (e – p); E 10 (e – p); E 20 (p); E 10 (p); E 25 (p); E 30 (p); M 15 (p)	O
Case 8	2	M	O 35 (e – p); E 35 (e – e + p)	M
Case 9	7	E+	E 35 (e – p); E 35 (e – p); E 35 (e – p); M 40 (e – p); E 40 (p); E 35 (e – p); E 50 (p)	E
Case 10	2	E	O 40 (p); E 35 (e – p)	O
Case 11	8	E	E 35 (e – p); E 35 (e – p); E 35 (e – p); E 35 (e – p); E 35 (p); E 50 (e + p); M 50 (e + p); E 40 (e + p)	O
Case 12	6	E	E 35 (e – e + p); O 35 (p); E 30 (p); M 50 (p); E 35 (e – e + p); E 45 (e – p)	O
Case 13	8	E+	M 35 (p); M 35 (p); E 35 (p); M 35 (p); E 50 (p); M 50 (p); O 50 (p); M 50 (e + p)	O
Case 14	2	E	O 10 (e – p); E 15 (e – p)	O
Case 15	7	E+	E 35 (p); E 30 (e – p); O 20 (e – p); M 35 (e – p); O 35 (e – e + p); E 35 (e – e + p); O 35 (e – e + p)	E
Case 16	6	E+	M 35 (p); E 45 (p); E 45 (p); O 45 (p); E 30 (p); O 50 (p)	E
Case 17	5	E	E+ 30 (p); E+ 35 (e – e + p); O 35 (p); E 25 (e – e + p); E 45 (e + p)	O
Case 18	3	E	E 35 (e – e + p); E 35 (e – e + p); E 35 (e – e + p)	O
Case 19	3	M	M 65 (e + p); E 45 (e – e + p); P 40 (e + p)	O
Case 20	2	E	M 50 (e – p); E 35 (e – p)	O
Case 21	4	E+	O 30 (e – p); M 25 (e – p); M 40 (e – e + p); E 30 (e – p)	O
Case 22	4	E	O 15 (p); E 60 (p); O 40 (p); M 40 (e + p)	O
Case 23	5	E	E 10 (e – p); E 20 (e – p); M 20 (e – p); M 40 (e – p)	M

*The endometrial findings are designated by the symbols, E, E–, E+, M and P as explained in the text. When O appears instead of these symbols, no endometrial specimen was obtained. The numerals following the endometrial symbols, indicate the amount of progesterone in mg. given prior to the time the specimen of endometrium was obtained. There follow next symbols denoting the character of treatment; (e – p) estrogens followed by progesterone; (e – e + p) estrogens followed by estrogens and progesterone given concurrently; (e + p) estrogens and progesterone given concurrently; and (p) progesterone given alone.

During treatment the following frequency of the endometrial findings occurred:

E (persistent estrogenic)	70	occurrences
E+ (hyperestrogenic)	3	occurrences
E- (hypoestrogenic)	4	occurrences
M (mixed)	21	occurrences
P (progestational)	1	occurrence
Total	99	occurrences

After the discontinuation of treatment, in 15 of the 23 patients, the following findings occurred:

E (persistent estrogenic)	4 patients
E- (hypoestrogenic)	1 patient
M (mixed)	2 patients
Total	7 patients (8 failed to return for examination)

The endometrial findings during therapy of the 4 patients who had mixed (M) endometria prior to treatment may be summarized as follows: a total of 3 specimens of the entire 17 examined showed progestational reaction (2M and 1P).

The therapy which preceded each specimen, in which some degree of progestational response was observed, may be analyzed as follows:

Treatment with estrogens followed by progesterone	8 instances
Treatment with estrogens followed by estrogens and progesterone	1 instance
Treatment with estrogens and progesterone	5 instances
Treatment with progesterone, alone	8 instances
Total occurrences of M and P	22 instances

The total doses of progesterone which preceded the finding of a M or P endometrium were as follows:

15 gm.	1 instance	40 mg.	6 instances
20 mg.	1 instance	50 mg.	5 instances
25 mg.	2 instances	65 mg.	1 instance
35 mg.	6 instances		
		Total	22 instances

The average dose of progesterone which was associated with a progestational response (M and P) was 38.6 mg. (Somewhat higher than the average dose given, 34.5 mg.)

DATA FROM DETERMINATIONS OF URINARY TITERS OF SODIUM PREGNANDIOL GLUCURONIDE

These data are based upon 40 cycles of 7 patients who had received cyclic therapy similar to those reported in Table I. Since 4 of these patients (Cases 3, 7, 22, and 23) were studied for endometriotropic responses, their records have been included also in Table I. The significant data secured from 6 of these 7 patients (Cases 3, 7, 22, 23, 24, and 25) are presented graphically together with brief protocols in Figs. 1 to 3.*

*The dosage of progesterone in these charts is given in terms of international units. One international unit of progesterone is equivalent to 1 mg.

Case 26 is presented only by protocol: (The record of this patient has been reported previously by our group.[24]) She was a white girl, aged 17 years, who was referred for the treatment of delayed adolescence and menarche. Examination showed a developmental status comparable to the late juvenile epoch. The uterus and cervix corresponded in size and contour to this stage of development.

Preliminary therapy with an anterior pituitary extract, containing gonadotropic and thyrotropic fractions, yielded no significant clinical responses. Cyclic treat-
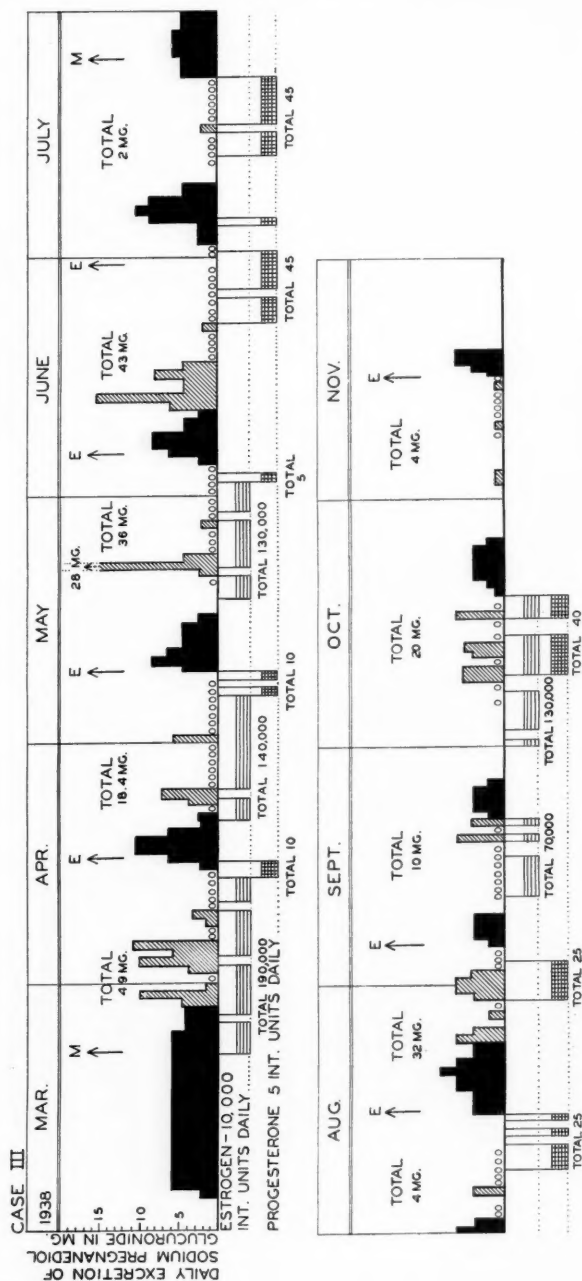
Fig. 1A.—Case 3.* A colored woman, aged 22 years, married, para 0-0-0, had had no metrorrhagia except that charted. Her period preceding the episode of bleeding in March had occurred February 18 and lasted until February 22. Endocrine and gynecologic surveys showed nothing significant. Treated cyclically with sterols as charted. Treatment was discontinued in October.

Explanation of symbols and abbreviations used in Figs. 1, 2, and 3. Curettage is indicated by ↓, biopsy by ↑. Menstrual flow is indicated quantitatively in terms of saturated pads by the solid black blocks. The urinary excretion of sodium pregnandiol glucuronide is shown by the shaded blocks. When determinations were made and negative values obtained, these are indicated by 0. Endometrial findings are indicated by E–, E, E+, M and P, the significance of which has been explained in the text.

The March to June cycles in Case 3 and January to June cycles in Case 7 have been reported previously by one of us (E.C.H.: Endocrinology 24: 13, 1939).

ment with the ovarian sterols was given.   During this treatment daily twenty-four-hour specimens of urine were studied for titers of sodium pregnandiol glucuronide.

Treatment was given as follows: from April 13 to 28 inclusive, 10,000 I. U. of estrogen (estrone) were given intramuscularly daily, resulting in a total dosage of 140,000 I.U.   From April 29 to May 6, inclusive, 5 mg. of progesterone were given intramuscularly daily, making a total dosage of 35 I.U.   From May 13 to 20, inclusive, 20,000 I.U. of estrone were given intramuscularly daily and from May 21 to May 28, inclusive, 10,000 I.U. were administered similarly, making a total dosage of 200,000 I.U. of estrone.   No bleeding followed these treatments despite the fact that some enlargement of the breasts and uterus occurred.
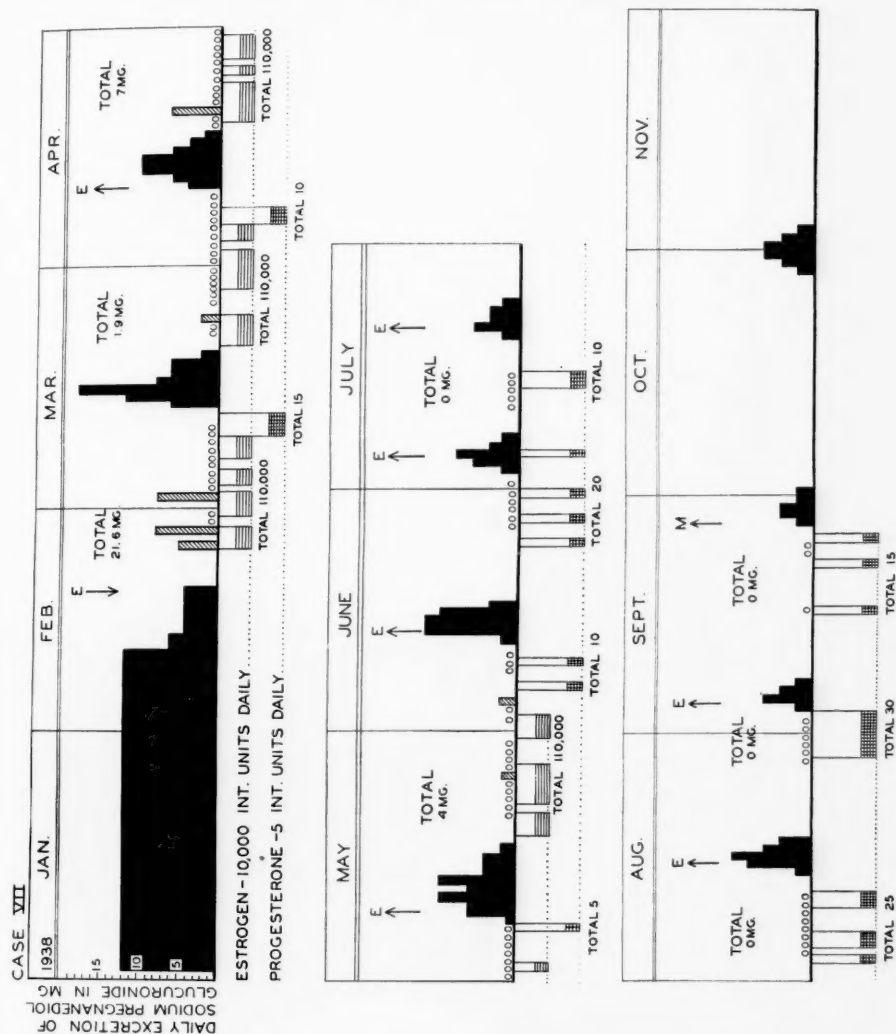

Fig. 1B.— Case 7.*   A colored woman, aged 20 years, single, had had excessive and depleting metrorrhagia for one year.   She was admitted to hospital February 9, at which time her hemoglobin was 11 per cent and erythrocytes 1,150,000.   After multiple transfusions, a curettement was done February 16.   Endocrine and gyne-cologic surveys were not significant.   Treated cyclically with sterols as charted.   Treatment was discontinued in September.

*See footnote to Fig. 1A.

All daily urinary specimens were consistently negative for sodium pregnandiol glucuronide during the entire period of therapy.

The data secured from the determinations of the urinary titers of sodium pregnandiol glucuronide of 7 patients are presented in Table II.
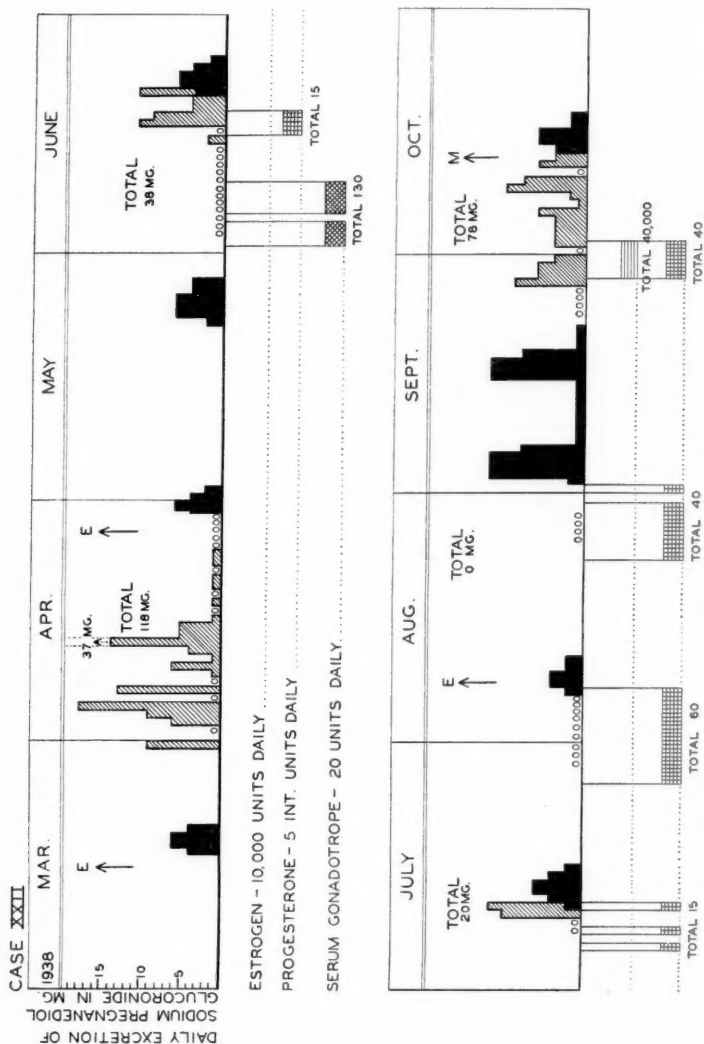

Fig. 24.—Case 22. A white woman, aged 30 years, married, para 0-0-0, had had absolutely irregular bleeding since menarche at 13 years of age. Intervals between episodes of flowing varied from five weeks to three months. Flow usually lasted three to five days and was not excessive. Patient sought treatment because of presumed sterility during her six years of marriage. Endocrine and gynecologic surveys yielded no significant findings. The cycle in June, when gonadotropes were given, is not considered in the data reported. Treatment has been discontinued.

The details of therapy have been discussed and are demonstrated graphically in Figs. 1 to 3. Combinations of estrogens (estrone and estradiol benzoate) with progesterone were employed for their presumed synergistic effects upon the utilization and metabolism of progesterone. Estriol or estriol glucuronide were not employed, although the recent studies of the Smiths[27] indicate a possible close association of this estrogen with the metabolism and utilization of progesterone. In collecting the data summarized in Table II from those presented in Figs. 1 to 3, an arbitrary system of selection was carried out as follows: No therapy was counted if urines were not available for at least twenty-four hours after it was given; all

sodium pregnandiol glucuronide excreted for seventy-two hours after the last injection of progesterone was credited to therapy.

All of the patients, except the one described in Case 26, excreted sodium pregnandiol glucuronide derived from their endogenous sterols. The larger number of determinations, done during times when no progesterone was given, was designed to estimate and evaluate this source of the pregnandiol-complex.
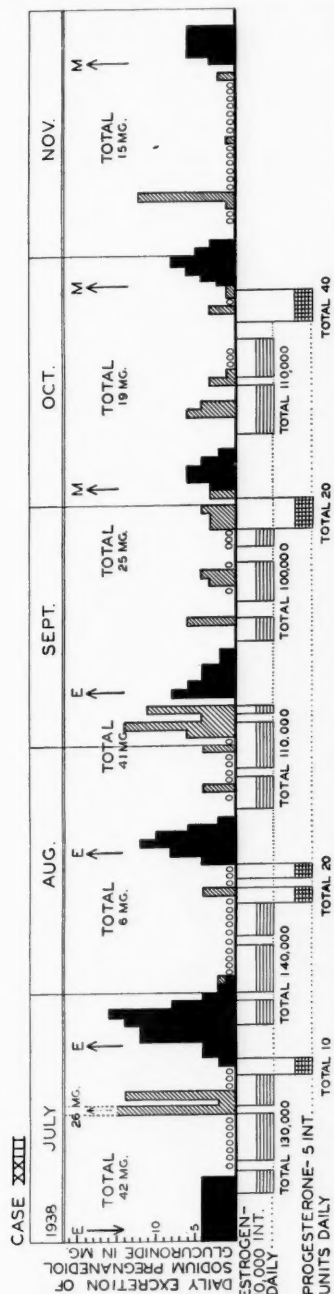

Fig. 2B.—Case 23. A colored woman, aged 17 years, single, had had polymenorrhea and hypermenorrhea for two years. A prolonged and depleting episode of metrorrhagia which began in January, 1938, lasted until curettage in July (see chart). At the time of admission to hospital July 1, 1938, the hemoglobin was 18 per cent and the erythrocytes were 1,950,000. Endocrine and gynecologic surveys yielded no significant data. Treatment with sterols was discontinued in October.

Selective segregation of these data indicates that during the time when 340 mg. of the 435 mg. of progesterone administered alone was given, no pregnandiol-complex was recovered in the urine.

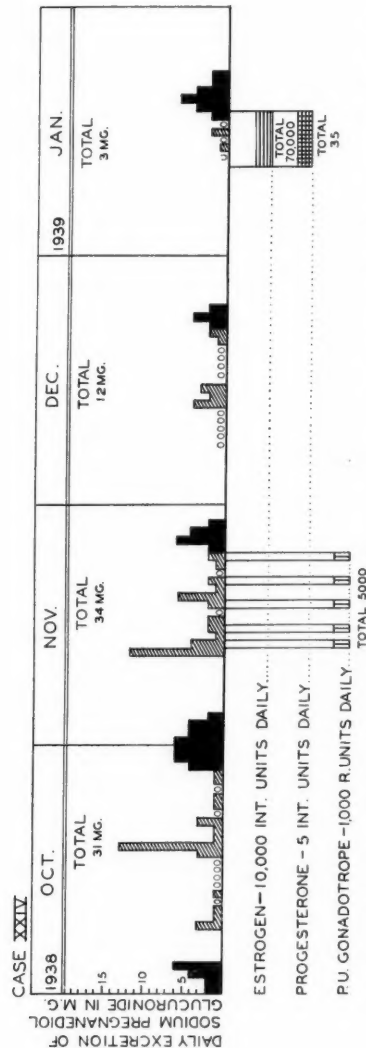The endometrial findings in Cases 3, 7, 22, and 23 have been summarized in Table I.

Fig. 3A.—Case 24. A white woman, aged 31 years, married, para 1-0-1, had had hypomenorrhea for some six years and for eighteen months had gained weight, had had a moderate hypertension and had experienced an itchy erythema of face, upper arms, and chest. Endocrine survey led to a tentative diagnosis of early pituitary basophilism. Gynecologic examination yielded no significant data. The month of November, when treatment with PU gonadotropes was carried out, is not included in the data reported. Treatment with sterols continues.

DISCUSSION

In a previous communication[25] we have referred to the effectiveness of cyclic therapy with the ovarian sterols in functional menometrorrhagia. The additional patients reported in this study give further proof of this desirable clinical response. It was suggested in the previous report that the effect of this form of therapy was exerted probably to a large degree upon the functional capacity of the pituitary.

The endometriotropic responses to it have not been striking. A study of these for evidence of effective utilization of injected progesterone is our present concern.

The dosage of progesterone employed has been essentially that adopted generally as the amount deemed necessary for producing a full progestational response of the endometrium. Some authors[28] have
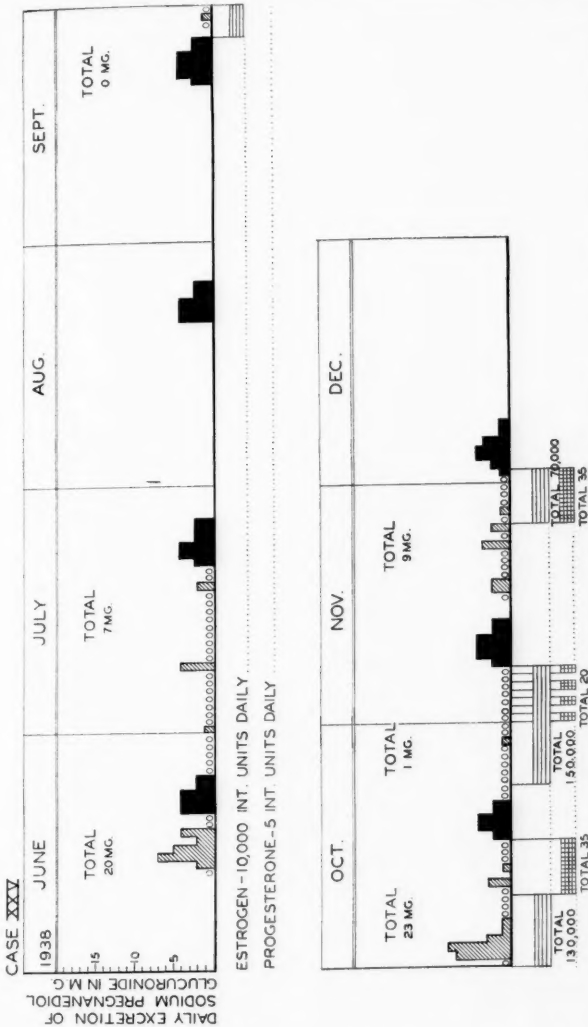

Fig. 3B.—Case 25. A white woman, aged 34 years, married, para 0-0-0, had had epileptiform convulsions in association with menstruation for two years. Endocrine, neurologic and gynecologic surveys yielded no significant data except for a low urinary titer of sodium pregnandiol glucuronide. There was a history of oligomenorrhea with episodes of amenorrhea during the eighteen months, prior to the time covered in the chart. The menses charted, however, were quite regular. Treatment with sterols was discontinued the first of December.

accepted the doses employed by Kaufmann[19] and Clauberg[18] as representing the possible cyclic output of the corpus luteum. The average dose for a series given by us has been 34.5 mg., one in good agreement with the theoretical amount necessary. During only 24 of the 117 cycles reported was the total dose less than 30 mg. An analysis of the doses which preceded the occurrence of some degree of progestational alteration does not indicate that the amount given was too small.

TABLE II.   DATA SECURED FROM STUDIES OF URINARY TITERS OF SODIUM PREGNANDIOL GLUCURONIDE OF 7 PATIENTS WHO RECEIVED CYCLIC THERAPY WITH OVARIAN STEROLS

THERAPY	AMOUNT OF PROGESTERONE GIVEN	AMOUNT OF ESTROGENS GIVEN	SODIUM PREGNANDIOL GLUCURONIDE				
			NUMBER OF DETERMINATIONS MADE	AMOUNT ACTUALLY RECOVERED	AMOUNT TO BE EXPECTED* IF METABOLISM AND RECOVERY WERE COMPLETE	PER CENT OF THEORETICAL YIELD ACTUALLY RECOVERED	AVERAGE RECOVERY PER DETERMINATION
	Mg.	I.U.		Mg.	Mg.	%	Mg.
Progesterone alone	435		95	61.0	739.5	8.2	0.64
Progesterone and estrogens given concurrently	140	270,000	29	37.0	238.0	15.5	1.27
Estrogens alone	0	1,990,000	216	285.4			1.32
No medication	0	0	186	340.0			1.84
Progesterone given but not correlated with the output of pregnandiol-complex	60						
Total	635	2,260,000	526	723.4			

*This is calculated upon the assumption that each molecule of progesterone (molecular weight 314) is converted into a molecule of sodium pregnandiol glucuronide (molecular weight 536), thus, amount of progesterone in mg. × 536/314 or 1.7 = amount of sodium pregnandiol glucuronide in mg.

A spread of treatments over a longer range of the cycle may prove more effective.

The endometriotropic effectiveness of this dosage when given in the manner described was only approximately 1 per cent, if the development of a generalized progestational response is accepted as a measure of it: only 1 normal progestational endometrium was encountered during the 99 cycles of therapy, the results of which were sampled by endometrial biopsies at the appropriate time.

If one accepts the occurrence of any evidence of progestational response (the presence of mixed endometria, having localized, patchy areas of progestational alteration), then the effectiveness of this therapy is approximately 22 per cent, for 22 mixed and progestational endometria were encountered after the 99 cycles of therapy.

This apparent ineffectiveness of progesterone does not seem definitely related to the lack of endometrial "priming" by estrogens.   The concurrent administration of estrogens and progesterone is apparently the most effective form of therapy.   It was employed only 9 times, resulting in some progestational alteration in 5 instances.   The concurrent administration of estriol or estriol glucuronide and progesterone was not done.   It should be tried.

The apparent inability of progesterone to be utilized effectively by the endometria of these patients for progestational alterations may be

related either to a refractivity of these endometria, or to the lack of some factor necessary to render utilization possible, or to the fact that progesterone cannot be metabolized and utilized when given in the form and manner generally employed clinically. The data secured from studies of the urinary titers of sodium pregnandiol glucuronide have some bearing upon these possibilities just mentioned.

In the instances of 6 of the 7 patients, whose urinary titers of sodium pregnandiol glucuronide were investigated, there is no reason to assume that any factors existed which disturbed the normal metabolism of progestin, for all of these 6 patients excreted varying amounts of the pregnandiol-complex before any treatment was given. The source of this must be related to the existence of an effective mechanism for the metabolism of the intrinsic progestin supplied by their own ovaries. These patients, however, as a study of their endometriotropic responses indicates, were not utilizing their own progestin effectively. There was either some necessary factor for this which was absent or a refractivity of the endometria existed. It may be assumed that similar conditions may have existed in some of the other patients not investigated in this regard.

Since these patients were able apparently to metabolize their own intrinsic progestin, it would be expected that they would be able to metabolize also that injected intramuscularly as progesterone. We have reported,[24, 29] however, that there exists some evidence that this extrinsic progesterone is not metabolized. Stover and Pratt,[30] furthermore, have reported the injection of 15 and 17.5 rabbit units of progestin as contained in an extract of corpora lutea (lipo-lutin) without being able to recover any of the pregnandiol-complex from the urines of the patient, although they carried out determinations for 12 consecutive days after the last injection. They call attention, however, to the fact that Venning and Browne[31] had reported that they had injected 19, 28, and 30 mg. of progesterone in 3 different women with recoveries of the pregnandiol-complex comparable to a yield of 46, 40, and 12 per cent, respectively.

Our data do not indicate that the progesterone given intramuscularly to the 7 patients reported was metabolized in such a manner as to result in any significant increases in the urinary titers of sodium pregnandiol glucuronide. Despite an intrinsic output of the pregnandiol-complex, the amount recovered during the administration of progesterone alone was equivalent to only 8.2 per cent of the theoretical yield to be expected from the metabolism of the extrinsic progesterone. When estrogens were given concurrently with progesterone, the total yield of the pregnandiol-complex was only 15.5 per cent of that to be expected from progesterone given had it all been metabolized into sodium pregnandiol glucuronide.

Similar differences apparently exist when the average recovery for each determination is examined: during the administration of progesterone this figure was 0.64 mg., while during the administration concurrently of estrogens and progesterone, it was 1.27 mg. When,

however, it is recalled that the average recovery for each determination was 1.32 mg. when only estrogens were given and 1.84 mg. when no therapy was given, it seems warranted to conclude that apparently no definite metabolism of the progesterone injected alone occurred. During its administration, as a matter of fact, there is a possibility that a depression of the metabolism of intrinsic progestin resulted.

The endometriotropic data and, perhaps, those concerned with the urinary titers of the pregnandiol-complex possibly indicate that the occurrence of a more effective metabolism and utilization of progesterone when it and the estrogens are given simultaneously. Recent studies on rabbits emphasize close correlations in the functions of these two groups of sterols: Courrier and Kehl[32] have reported that the involution of a progestational endometrium, which occurs despite continued injections of progesterone, is retarded by the simultaneous administration of estradiol and progesterone; Heckel and Allen[33] have found that injections of estrogens during the latter part of pregnancy result in an inhibition of parturition, apparently due to a maintenance of the functional capacity of the corpus luteum.

Since, however, the average recoveries of the pregnandiol-complex per determination during the administration of estrogens and during that of estrogens and progesterone conjointly were practically identical, one may assume that any alterations were due to effects exerted by the estrogens on the metabolism of the intrinsic progestin of these patients. The high value of the average recovery of the pregnandiol-complex during the intervals when no treatment was given is probably not significant, since it is due to the inclusion of data secured from the long first cycle of Case 22 when an unusually large amount (118 mg.) of the pregnandiol-complex was excreted.

Venning and Browne[34] have reported that in some instances the conjoint administration of progesterone and pregnancy-urine gonadotropes resulted in a greater excretion of the pregnandiol-complex than when progesterone alone was given. Our group[35] has made similar observations, and we have encountered in some instances striking enhancement of these values when estrogens, pregnancy-urine gonadotropes and progesterone are given simultaneously.

Many of the difficulties which are apparent in attempts to evaluate the data presented in this study would not be encountered in a group of women having no metabolism of their intrinsic progestin. For this reason, similar studies should be made upon oophorectomized women.

SUMMARY

Studies have been reported upon the endometriotropic responses of 23 patients with functional irregularities of uterine bleeding during 99 of 117 cyclic series of therapy with progesterone alone or combined with estrogens. During 30 cycles of 4 of these patients, and during 10 cycles of an additional group of 3 patients, similarly treated, urinary titers of sodium pregnandiol glucuronide were determined.

The endometriotropic data warrant the conclusion that crystalline progesterone, when administered intramuscularly in oil to women with functional irregularities of uterine bleeding, is inefficiently utilized. Six of the 7 patients studied were also unable to utilize efficiently their intrinsic progestin despite the existence of evidence that it was being metabolized normally.

The intramuscular administration of crystalline progesterone to these patients resulted not only in no increases in their urinary titers of the pregnandiol-complex but also in apparent decreases. These observations suggest that incomplete metabolism occurred.

Some of the various factors which may influence the metabolism and utilization of progesterone are discussed.

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TOXEMIA MORTALITY IN THE SOUTHERN STATES*

A CRITICAL STUDY OF 577 MATERNAL DEATHS IN NORTH CAROLINA
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THE percentage of maternal deaths in the South from the toxemias of late pregnancy is strikingly high when compared to other sections of the United States, and presents a peculiar sectional problem worthy of consideration. The map (Fig. 1) of the United States, prepared by the Children's Bureau of the United States Department of Labor, presents in a clear-cut manner the "toxemia belt" as related to maternal mortality. In a group of eight adjoining southern states nearly one-third of all maternal deaths are due to the toxemias of late pregnancy (Fig. 1).

Fig. 1.—Percentage of maternal deaths from eclampsia and other toxemias, 1933 to 1935. (U. S. Dept. of Labor, Children's Bureau.)

It was believed that a study of atmospheric conditions in various states of the Union and their comparison with these southern states, together with a detailed analysis of a large number of maternal deaths from late pregnancy toxemia in one southern state, might disclose factors contributing to this appalling loss of maternal life and its sectional distribution.

With the aid of the United States Weather Bureau, the average rainfall of each state in the Union was ascertained, together with

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average monthly temperature, humidity, percentage of sunshine, etc. It became immediately apparent that the percentage of maternal deaths from toxemia of pregnancy was highest in those states with the highest annual rainfall, but only where the season of rainfall was accompanied by a relatively high temperature. It was found to be generally true that the southern states had a high temperature during the months of greatest precipitation, and it is in these states that toxemia exacts its terrific toll (Florida, Louisiana, Virginia, Tennessee, North Carolina, etc.).

Upon investigating average monthly temperatures in other sections of the country, it was found that a reduction of rainfall during the hot months or heavy precipitation during the colder months was the trend in states with a low maternal mortality from toxemia. For example, both Washington and California, while states with a high precipitation, have a low temperature during the months of greatest rainfall and only a small percentage of the maternal deaths in these states is due to toxemia (Figs. 2 and 3). Also states that are naturally dry throughout the entire year, such as Colorado, have a small percentage of their maternal deaths from toxemia. As the rainfall increases with rising temperature, the tendency is toward an increase in fatal toxemia (Illinois, Indiana).

Another exception to the general trend of a high percentage of maternal deaths from toxemia in states with heavy rainfall associated with high temperature was found in those states with highly organized and well-advanced maternal welfare programs. In this classification are states with concentrations of population, as New York with 11.1 per cent of maternal deaths from toxemia, New Jersey 11.8 per cent, and Pennsylvania 13.3 per cent. It was impossible to establish any relationship between humidity, sunshine, and eclampsia. These findings are somewhat confirmatory of Dieckmann's[1] conclusions that eclampsia flourishes in a hot, wet climate.

In 1932 the Bureau of Vital Statistics of the North Carolina State Board of Health initiated a five-year study of maternal deaths in North Carolina. A detailed questionnaire was sent to every physician who signed a death certificate on which some condition relating to pregnancy was given as the cause of death. Of the 2,746 questionnaires, 58 per cent were returned with acceptable information. A total of 577 questionnaires reporting eclampsia, hypertension, albuminuria, or other toxemias of pregnancy as the cause of death were personally studied in detail and form the basis of the statistical data herein reported (Fig. 4).

There were 344 fatal cases of eclampsia and 171 nonconvulsive fatalities from late pregnancy toxemia with albuminuria and/or hypertension, which, together, accounted for 32.3 per cent of all the maternal deaths reported. There were 62 additional fatalities classified as due to "other toxemias of pregnancy," which, according to this survey, constitute 3.9 per cent of the maternal deaths in North Carolina.
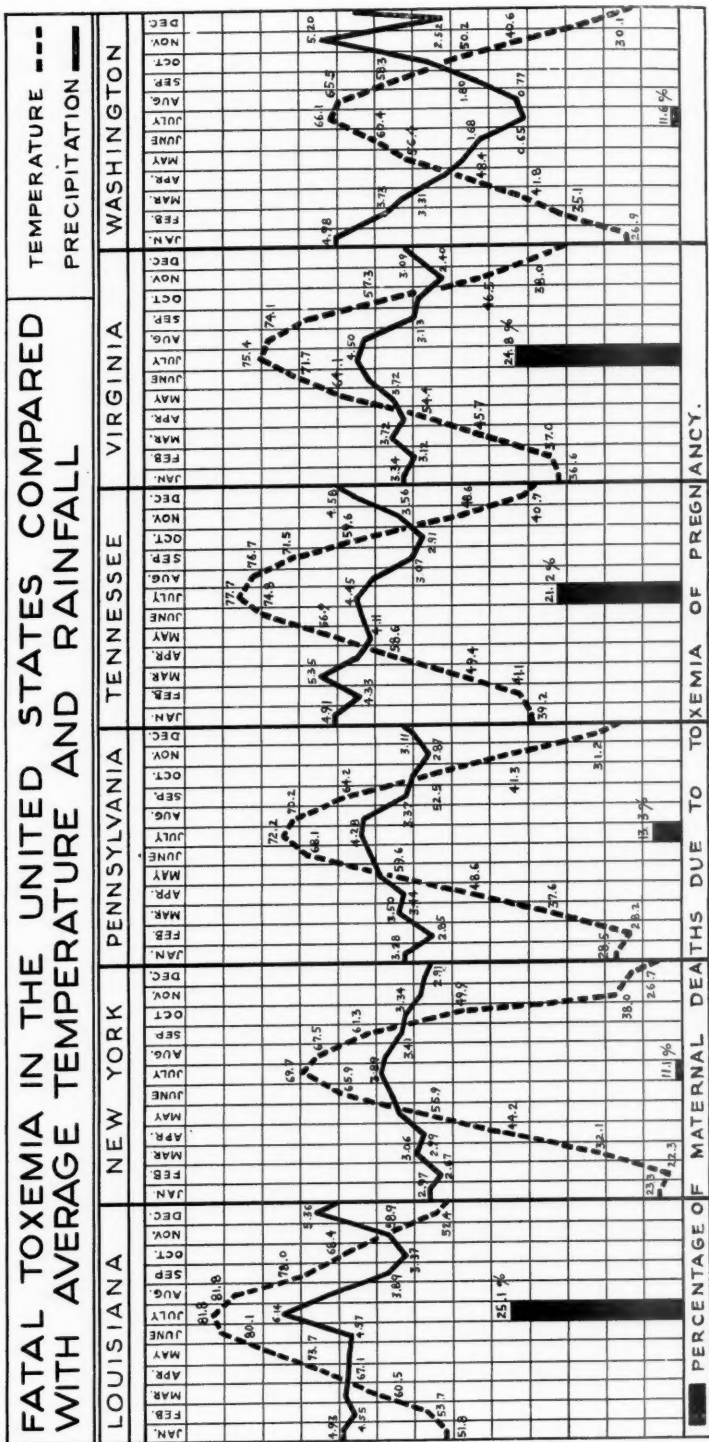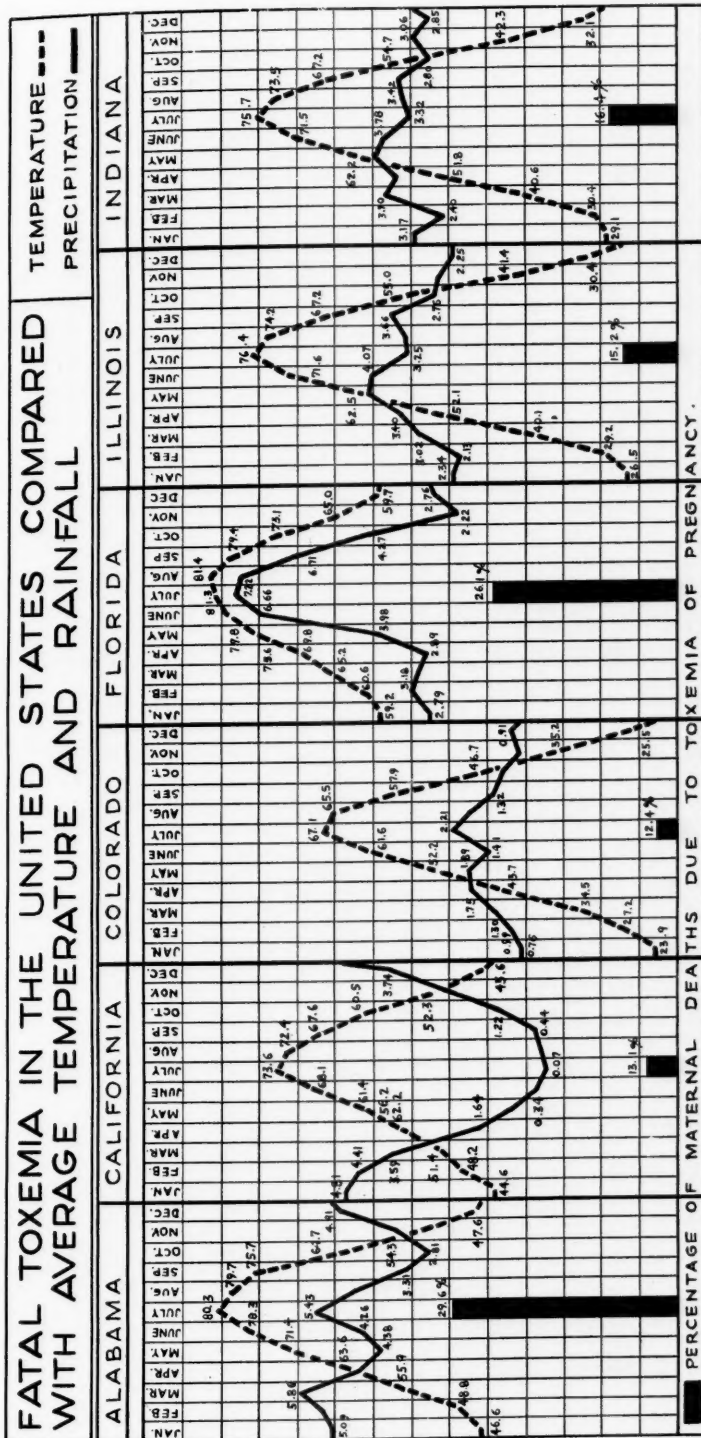
Fig. 2.

Fig. 3.

The high percentage of maternal deaths from puerperal albuminuria and particularly eclampsia in North Carolina, as found by this detailed investigation, is in accord with the findings of other investigators who have repeatedly reported the high incidence of convulsive toxemia in the southern states.[2-4]

344 MATERNAL DEATHS FROM ECLAMPSIA IN NORTH CAROLINA

The 344 maternal deaths from eclampsia were separated into the months in which death occurred, and a chart prepared showing this in relation to the average monthly temperature and rainfall in North Carolina. It is evident that there were more fatal eclamptic cases during the months of greatest precipitation and temperature, but quite apparent that the distribution of death permits of many other factors and causes (Fig. 5).

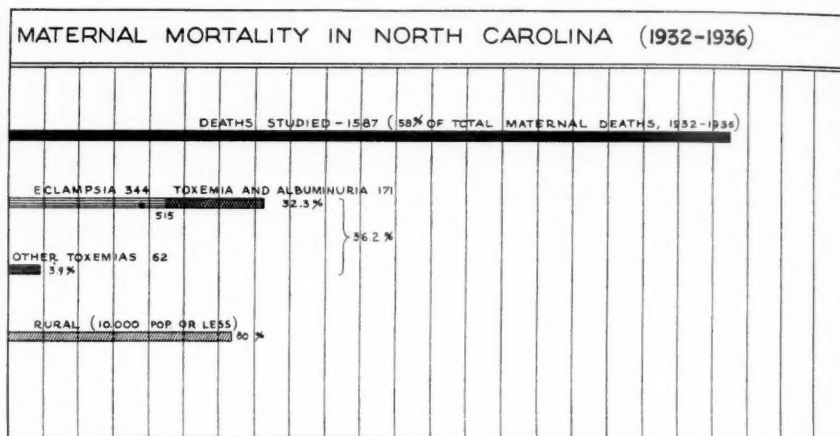MATERNAL MORTALITY IN NORTH CAROLINA (1932-1936)

Fig. 4.

Fifty-one per cent of the 344 eclamptic patients died in North Carolina hospitals. During the past ten years there has been an increase in the percentage of hospital births in North Carolina from 5 per cent to approximately 20 per cent. According to the hospital section of the Duke Endowment, in 1926 there were 150 patients with eclampsia hospitalized in North Carolina, constituting 4.7 per cent of the hospital deliveries, with 35 maternal deaths, an eclamptic mortality rate of 23.33 per cent. In 1937 there were 332 cases of eclampsia, constituting 2.8 per cent of a total of 11,704 hospital births with 41 fatalities, an eclampsia mortality rate of 12.35 per cent (Fig. 6).

In 1926, 51 per cent of all maternal deaths occurring in North Carolina hospitals were due to eclampsia. With the increase in the number of hospital births and probably aided by a more conservative treatment of the active eclamptic patient, there has been a gradual reduction of this figure. In 1937, in the 81 nonprofit hospitals operated under the Duke Endowment, 29 per cent of all the maternal deaths were reported as due to eclampsia.

Eighty per cent of the fatal cases of eclampsia in North Carolina occurred in rural areas or in towns of less than 10,000 population. As 85 per cent of the population of North Carolina is found in communities of 10,000 or less, this figure is commensurate with the distribution of population. Hospitalization of the 163 institutional deaths was a last resort in many patients who arrived in extremis. One institution with a large obstetric service reported a total of 3 fatal cases of eclampsia in five years, the deaths occurring one, two, and five hours, respectively, after hospital admission.

Only 6 patients of the 344 fatal cases of eclampsia had adequate and good pre-
natal care, apparently dying of an overwhelming fulminating convulsive toxemia.
Sixty (17 per cent) had negligent or inadequate prenatal care.   While it is im-
possible to establish accurately the responsibility for this group of 60 maternal
deaths of patients who were under medical supervision, the basic factors were
apparently well distributed between negligence on the part of the patient and
indifferent supervision on the part of the physician in the presence of warning
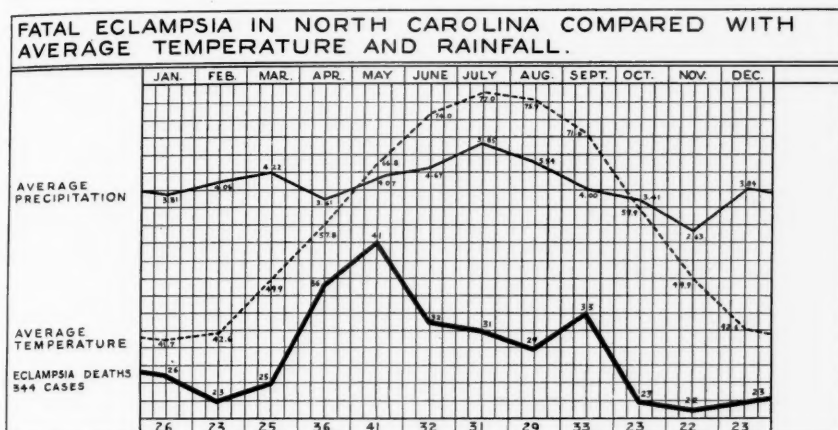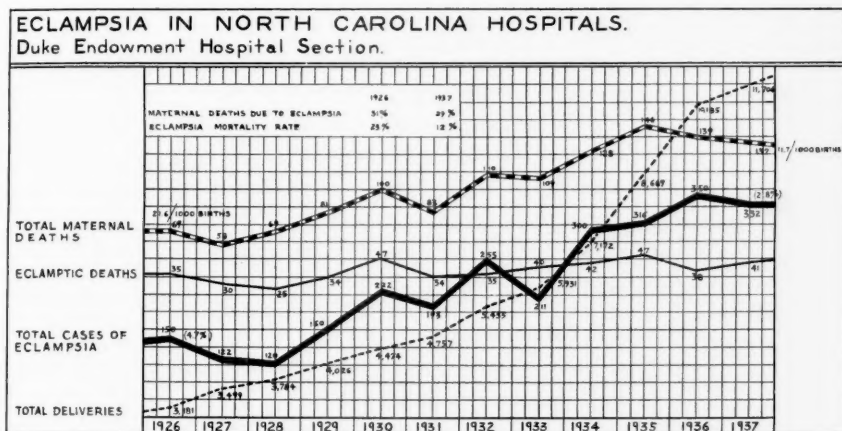symptoms and alarming physical findings.

Fig. 5.

Fig. 6.

The extreme inadequacy of the medical care obtained by these convulsive cases
is illustrated by the fact that 64 patients were undelivered at death and 4 were
dead upon the arrival of a physician.   One hundred and forty-four (42.7 per cent)
were in active convulsions at the time of their first medical contact.   Fifty-one
were in active labor at the time of their first medical contact, and 51 had been
delivered either unattended or by a midwife when a physician first arrived
(Fig. 7).

Illegitimacy and race were contributing factors in the maternal mortality
(Fig. 8).   There were 21.8 per cent (75 cases) illegitimate pregnancies, as com-

pared to 7.6 per cent illegitimacy of all births occurring in North Carolina in 1936. Forty-two and one-tenth per cent of the patients (144 cases) of the fatal cases of eclampsia were colored, as compared to a negro incidence of approximately 30 per cent of the annual births in North Carolina. Forty-four per cent of the 344 fatalities from eclampsia occurred in multiparas. Two out of 5 of these patients gave a definite history of toxemia in a previous pregnancy. Doubtless this figure would be higher with more complete and accurate histories.
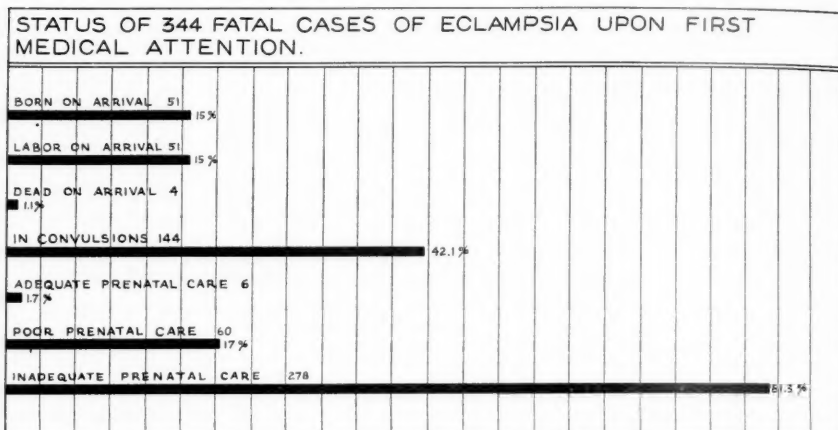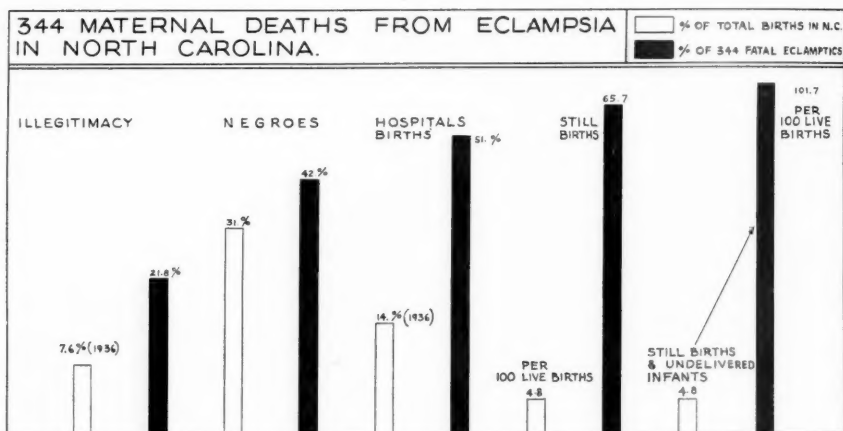

Fig. 7.

Fig. 8.

There were 245 infants delivered by physicians with a 50 per cent operative interference (Fig. 9). In 117 of the 122 operative deliveries, the only indication given for obstetric surgery was the pregnancy toxemia. The other indications consisted of hemorrhage in 4 cases and disproportion in 1. On these 122 cases, 175 operations were performed, consisting of 41 versions, 43 dilatations of the cervix, 38 low forceps, 13 midforceps, 9 high forceps, 10 cesarean sections, 3 breech extractions, 5 bag or bougie inductions, 6 cases of manual removal of the placenta, 6 extensive repairs, and 1 craniotomy. One patient died as a result of spinal anesthesia. Two deaths illustrate the danger of pituitary extracts in acute vascular spasm, as death immediately followed administration of pituitrin in one and thymophysin in another.

The high incidence of operative interference in those patients attended by a physician prior to delivery is a condemnation of the quality of medical care. A possible trend toward conservatism is indicated by the small number of cesarean sections (10). In spite of the fact that 64 eclamptic patients died undelivered, there were 2 post-partum deliveries of living children, 1 by cesarean section and 1 by forceps.

In 27 per cent of the 344 cases of eclampsia, the onset of convulsions was after delivery. It was impossible to separate accurately the remainder into ante- and intra-partum eclamptics.

The terrific infant mortality in this group is apparent. One hundred and thirteen infants (40 per cent) were stillborn, 172 were born alive, 62 were undelivered and the fate of 11 infants was unknown. The stillbirth rate was 65.7 per 100 live births, as compared to an average incidence over the state of 4.8 per 100 live births. The addition of the 62 undelivered infants gives a fetal mortality of 101.7 per 100 live births (Fig. 8). It was impossible to analyze the additional high infant mortality from neonatal deaths.
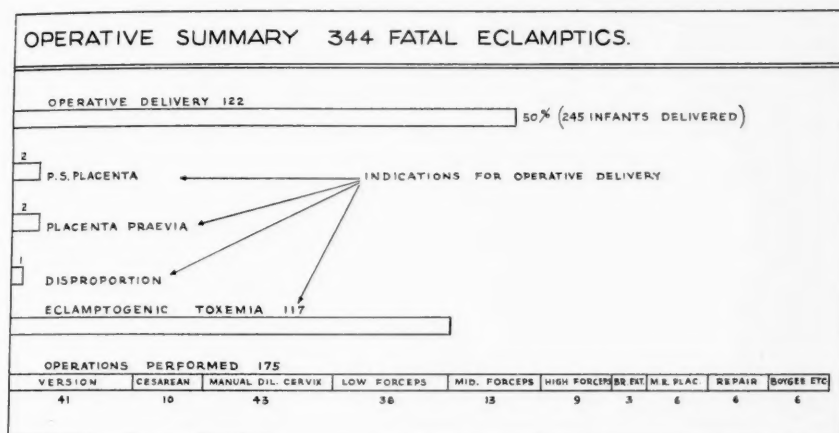

Fig. 9.

Other maternal complications include 16 cases (4.65 per cent) of twins, 9 cases of pneumonia, 3 cases of influenza, 2 cases of acute yellow atrophy of the liver, 2 cases of hyperthyroidism, 3 of diabetes, 1 of chronic mitral disease, 1 of malaria, 4 of post-partum hemorrhage, 2 of placenta previa, and 4 of premature separation of placenta.

171 MATERNAL DEATHS FROM LATE PREGNANCY TOXEMIA WITHOUT CONVULSIONS IN NORTH CAROLINA

A detailed study of the 171 fatalities from late toxemias with albuminuria and/or hypertension without convulsions reveals a higher incidence of multiparity and a greater predominance of patients in the later years of the childbearing period than in the 344 fatal cases of eclampsia. The importance of a history of eclampsia or toxemia in a previous pregnancy is further emphasized in this group, as 51 (48 per cent) of the 106 multiparas gave a definite history of previous toxemia of pregnancy (Fig. 10). When the inadequacy of prenatal care and the lack of complete obstetric history in this group of patients are considered, it is quite probable that even a higher percentage of the multiparas had toxemia in a previous pregnancy.

The striking contrast of the average age in this group as compared with the fatal cases of eclampsia is revealed in Fig. 11. Thirty per cent of these patients were forty years of age or over, as compared to 17 per cent of the eclamptics (Fig. 11).

There were only 10 illegitimate pregnancies, constituting 6.4 per cent of the deaths, which is no higher than the percentage of illegitimacy in the state as a whole, and contrasts strikingly with the 21.8 per cent of illegitimacy as found in the fatal cases of eclampsia.

Race is also apparently not a factor in the nonconvulsive maternal mortality, for of the 171 maternal deaths 31.5 per cent were negroes which is no higher than the percentage of colored births in North Carolina during the past five years.
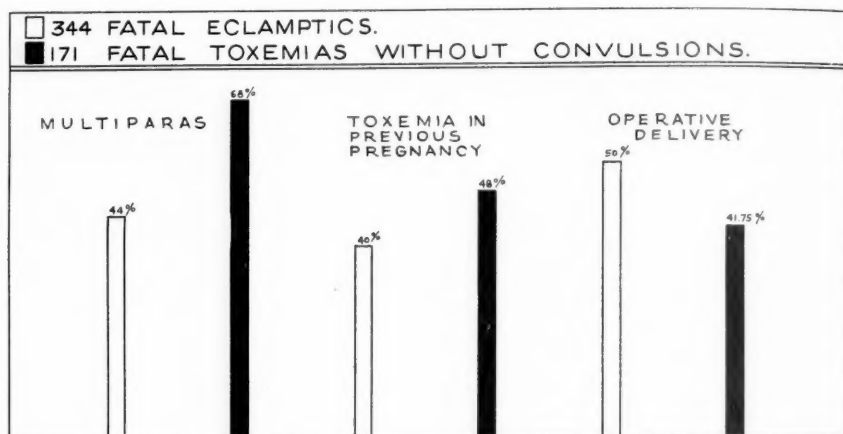

Fig. 10.
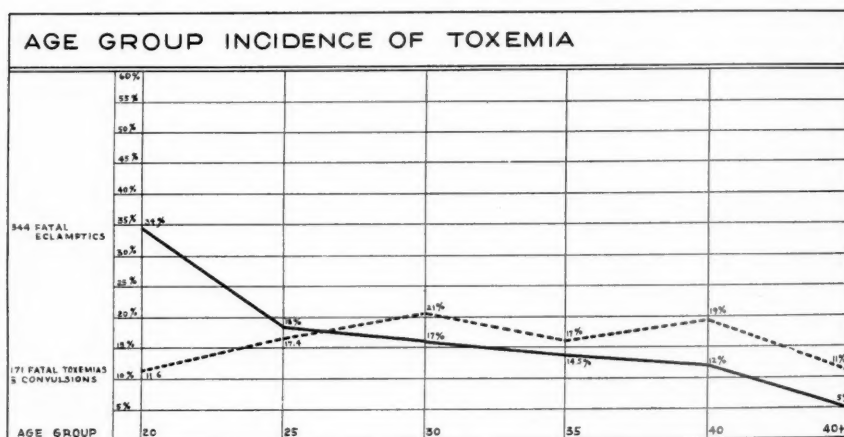
Fig. 11.

Sixty-three of these 171 nonconvulsive patients had a very acute form of hypertension, 58 had a more chronic hypertension, 7 had no hypertension, and in 43 the duration of hypertension prior to death was unknown. The amazingly high number of maternal deaths with an acute elevation of blood pressure without convulsions, coupled with the fact that in this group there were 40 deaths with acute pulmonary edema, is a striking confirmation of the fact as first reported by

Teel, Reid and Hertig[5] that acute, pre-eclamptic toxemia may suddenly terminate in a fatal form of ''cardiac asthma'' without convulsions.

From the questionnaires, it appears that multiple pregnancy and pulmonary infection were additional precipitating factors in many of the deaths from acute cardiac decompensation. In the entire group of 171 nonconvulsive deaths, there were 17 cases (10 per cent) of multiple pregnancy and 9 cases (5.3 per cent) of pneumonia.

The high incidence of premature separation of the placenta (4.6 per cent) and of post-partum hemorrhage (3.3 per cent) is confirmatory of the contributing part played by vascular disease in these two conditions. The comparison of this incidence with the incidence occurring in the 344 fatal cases of eclampsia and the average obstetric incidence is shown in Fig. 12.
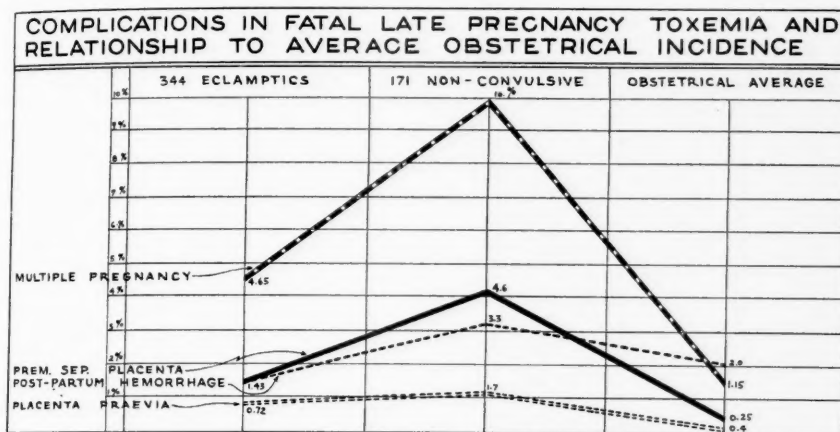
Fig. 12.
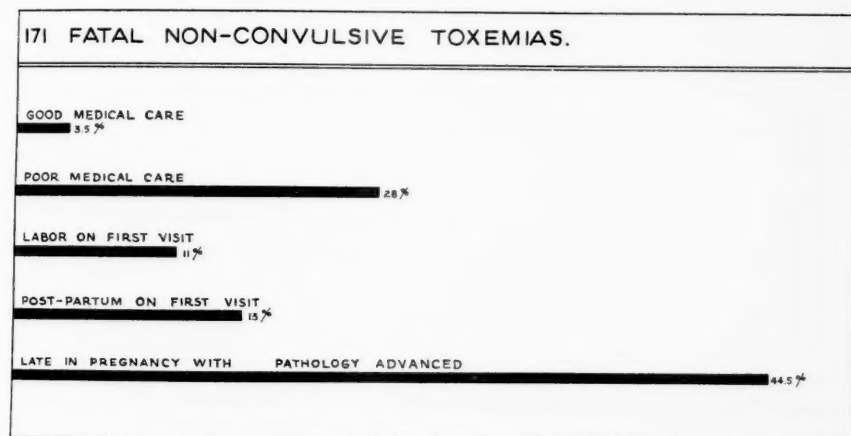
Fig. 13.

As would be expected from advanced vascular pathology, there were 15 cases of hemiplegia or cerebral hemorrhage, and one case of sudden death, probably also from cerebral hemorrhage, making a total of approximately 10 per cent of these maternal deaths due to an acute cerebral accident. There were 5 cases of uremia and 13 cases of acute nephritis. There were 2 cases of ileus. Additional complications include the following: pellagra 2, mitral disease 2, anesthesia death 1, ruptured uterus 1, inanition 1, and Vincent's angina 1.

The striking tendency toward operative interference is also present in this group of 171 nonconvulsive maternal deaths. Although 22 patients were delivered without a physician, 41 per cent of the remainder had an operative delivery. Fifty-seven operations were performed on 50 patients, consisting of 12 cesarean sections (24 per cent of all operations), 21 forceps, 10 versions, 10 surgical inductions of labor, and 4 manual dilatations of cervix. Seventy-five per cent of these deaths occurred in patients living in rural communities or in towns of less than 10,000 population. Fifty-four per cent of these deaths occurred in hospitals, as compared to 51 per cent of the fatalities from eclampsia.

There is a most striking loss of infants naturally to be expected in this group. The gross infant mortality rate (stillbirths and undelivered infants) was 110.5 per 100 live births. Thirty infants were recorded as being born alive but of less than seven months' gestation. The addition of these as neonatal deaths gives a loss of infant life of 280 per 100 live births. Only 57 of the 188 infants, including twins, are known to have had a chance for survival.
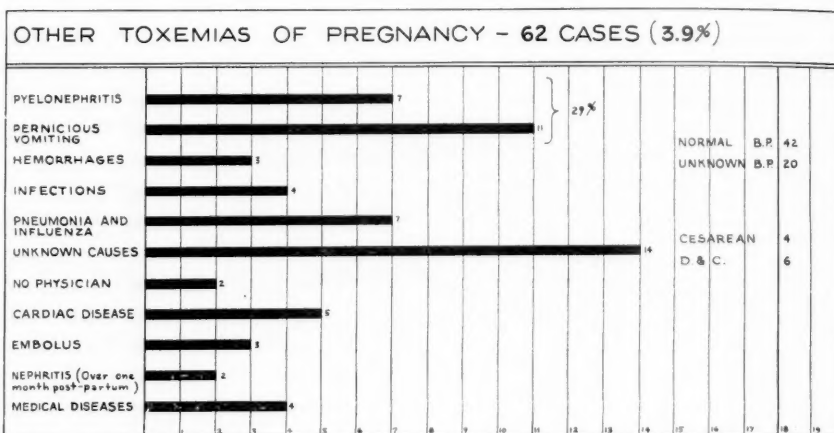

Fig. 14.

The inadequacy of medical care is also striking. Only 3.5 per cent of the 171 fatalities received competent medical supervision. In this group there was a pathetic lack of proper evaluation of physical findings on the part of the attending physician, as is shown by the fact that in 48 cases (28 per cent) prenatal care was administered by a physician who in the presence of either advanced vascular disease, gross albuminuria, or other portent physical findings, of from two weeks' to six months' duration, made no effort toward termination of the pregnancy (Fig. 13).

Lack of any prenatal care occurred as follows: 11 per cent of these patients were in labor upon the first visit of a physician, 44.5 per cent were seen for the first time by a physician late in pregnancy with gross vascular pathology, and 13 per cent received their first medical care after delivery.

62 MATERNAL DEATHS FROM "OTHER TOXEMIAS OF PREGNANCY"

An analysis of the questionnaires concerning maternal deaths classified as due to other toxemias of pregnancy (International classification No. 147) totals 62 cases which constituted 3.9 per cent of all the maternal deaths. Only a small percentage of these cases were correctly classified (Fig. 14).

There were 11 cases of pernicious vomiting of pregnancy and 7 cases of pyelonephritis, which, together, constituted 30 per cent of these maternal deaths. The remainder were found to be improperly classified, the probable causes of death being as follows: 16 (26 per cent) unknown causes, 7 pneumonia or influenza,

5 cardiac disease, 4 peritonitis or post-partum infection, 3 puerperal hemorrhage unassociated with toxemia, 3 pulmonary embolus, 1 intracranial tumor, 1 post-operative psychosis, 2 acute nephritis onset over one month post partum, 1 pan-sinusitis and 1 amyotrophic lateral sclerosis.

There were no known cases of hypertension in this entire group. Forty-one had normal blood pressure and in 21 the blood pressure was unknown. In this group of 62 cases, there were 4 deaths following cesarean sections and 6 patients died following termination of pregnancy by curettage.

This group of deaths is reported in detail to point out the faulty deductions that may be drawn from vital statistics. In 70 per cent of these deaths, although included as due to "other toxemias of pregnancy," the patients died either of unknown causes, of medical complications, or of obstetric pathology without toxemia.

SUMMARY

The high maternal mortality rate in the southern states from the toxemias of late pregnancy is possibly abetted by the hot, wet climate characteristic of this section of the United States. The graph study of 344 maternal fatalities in North Carolina from eclampsia classified according to the month of death as compared to the average temperature and rainfall, confirms or rather substantiates the greater danger of this disease during the hot, wet months of the year. A similar study of precipitation and temperature in various states in the country would indicate that there is less eclampsia in the dry climate and that heavy precipitation unassociated with high temperature is less likely to be accompanied by a high toxemia rate.

A detailed study of 515 maternal deaths from late pregnancy toxemia occurring in North Carolina during the years 1932 through 1936 reveals other and more important contributing factors than those of climate. First among these is neglect. Only 12 patients received adequate pre-natal care and competent medical supervision. Two hundred and fifty-two were seen for the first time by a physician late in their pregnancy, either in convulsions or with advanced toxemia. Seventy received their first medical attention when in labor, and 73 saw a physician for the first time after delivery. In 108 cases, there was prenatal care of an inadequate or faulty type.

This study confirms the fact as repeatedly stated by Stander, Acosta-Sisson, and others, that the toxic multipara with a history of toxemia in a previous pregnancy is a grave risk. Approximately 45 per cent of the multiparas in this study gave a definite history of toxemia in a previous pregnancy, a figure that is too low because of the fact that in-complete obstetric histories were obtained on many of the 515 fatalities.

This study also substantiates the additional likelihood of late preg-nancy toxemia in the presence of multiple pregnancy and the increased danger in acute upper respiratory or pulmonary infections. It calls attention to the additional risk of premature separation of the placenta and post-partum hemorrhage in the toxemias of late pregnancy, because of their increased incidence as complications of the disease.

The great danger of sudden cardiac decompensation in the acute pre-eclampsias, the surprisingly high incidence of cerebral hemorrhage (10

per cent) in the nonconvulsive toxemias, the high percentage of illegitimate pregnancy in fatal eclampsia (three times the incidence of illegitimacy in the state of North Carolina) are re-emphasized.

While the incidence of operative interference upon the grave toxemia was probably unnecessarily high and hence a factor in mortality, the other extreme, namely the policy of laissez-faire or lack of early active intervention in the presence of advanced vasculorenal disease, often accompanied by a bad toxemia history, was a much more vital contributing factor to maternal mortality.

The loss of infant life needs no further comment except to repeat that the approximate yield of living viable infants from the 515 maternal fatalities was less than 40 per cent.

The increasing trend toward hospitalization of obstetric cases in North Carolina in the past decade (from 5 per cent of all births in 1926 to 20 per cent in 1937) has been accompanied by a reduction of the maternal mortality from eclampsia, which has fallen from 23 per cent in 1926 to 12 per cent in 1937.

Social and economic factors are intimately woven into the maternal welfare problem in the southern states. In North Carolina approximately 85 per cent of the state's 3½ million population are rural or live in towns of less than 10,000. Thirty-two per cent of the births are delivered by midwives and many of the remainder who are delivered by a physician are not seen until in labor.

In conclusion, it is evident that the high maternal mortality rate from toxemia of late pregnancy in the southern states as represented by this analysis of 515 such deaths in North Carolina is primarily due to social and economic circumstances. A widely scattered and rural population, a high percentage of illiteracy, the inaccessibility of adequate prenatal supervision in the past in many remote sections, the failure of prompt utilization of hospital facilities and often the inaccessibility of competent obstetric consultation, and a midwife service untrained and poorly qualified, are among the contributing factors to this problem.

The social implications necessary to cure this cancer are particularly realistic at this time. Adequate and competent maternity care for every expectant mother is a problem vitally dependent upon the active cooperation and direction of organized medical forces.

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PREMATURE RUPTURE OF THE MEMBRANES AS A METHOD OF INDUCING LABOR*

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ADDITIONAL responsibility is placed upon physicians who work with people lacking environmental and educational advantages. This responsibility includes the making of many major medical decisions by the physician because the patient is unable to analyze the problem.

Our obstetric clinic, all colored and entirely charity, has approximately a 30 per cent incidence of hypertensions. We experience much difficulty in correctly classifying the so-called toxemias of pregnancy. This difficulty is increased because of our crowded service and inability to keep patients long enough for final decision. We admit that the classifications as used in this study are more or less inaccurate, but they were made with all the available evidence at hand and, for practical purposes, are useful. We think it conservative to say that in our clinic we practically never see an acute nephritis as a complication of pregnancy and that proved chronic nephritis is rarer than is generally believed.

Primary vascular disease seems to be the etiologic factor in most of the sustained hypertensions during early and middle pregnancy. Pre-eclampsia as diagnosed in our clinic usually means: a hypertension developing slowly or abruptly in the last trimester of pregnancy, edema, gain in weight, certain objective symptoms and signs and, in the majority of patients, localized spastic constrictions of the retinal arterioles. Albuminuria is not a constant finding. Chronic vascular disease, on the other hand, has in the majority of cases, only a hypertension. This hypertension is usually observed much earlier in pregnancy than the hypertension of pre-eclampsia. Changes in the retinal vessels are constantly present and will be described later. Physical examination and laboratory procedures are usually negative. A practical point that will often help in the differentiation of pre-eclampsia and chronic vascular disease is that bed rest, as a rule, does not lower the blood pressure in pre-eclampsia but does lower the blood pressure in chronic vascular disease. Our clinic believes that there is no expectant treatment for a *severe* pre-eclampsia and that labor should always be induced.

Naturally, a clinic with such a high incidence of hypertensions will show a high percentage of labor inductions. In this paper we wish to present our results with 322 consecutive inductions in which rupture of the membranes was the basic method used. We believe that there was a definite, legitimate indication for practically every induction. Malposi-

tion of the fetus was about the only contraindication recognized. We have no hesitancy in rupturing the membranes from the seventh month of gestation, and the station of the head was not considered. A long, rigid cervix was not a contraindication.

The precise method of induction was as follows: 223 castor oil, quinine, rupture; 7 quinine and rupture; 30 rupture alone; 4 rupture, pituitary extract; 2 bag, pituitary extract, rupture; 1 castor oil and quinine; 1 castor oil and rupture; 1 rupture and bag; and 3 castor oil, quinine, bag, rupture. In the majority the patient was given castor oil, two doses of quinine (5 gr. each), a hot enema, and the membranes were ruptured later. It is difficult to prove definitely that quinine given the mother kills the baby. That it may cause congenital deafness must be considered. We are much less inclined to use the drug in pregnancy and have discontinued its use in the induction of labor. As much care was exercised in the preparation of the patient and the physician as for a vaginal hysterectomy. The puncture was made with the instruments devised by DeLee and Wilson. If the amniotic fluid did not flow freely the head was partially displaced. Metaphen was instilled into the vagina at the time of rupture and every four hours during the latent period and labor. We believe that this procedure makes such an induction safer and is, at least in part, the answer to the rather low morbidity percentage in this series. A rule of the service is to administer pituitary extract only if labor has not started eight hours after the membranes have been ruptured. As a rule, the decision to use the drug is made by the resident on duty. Two minims are given with a tuberculin syringe every thirty minutes until uterine contractions commence. Never more than six doses are given. When uterine contractions start, the drug is stopped regardless of the number of doses given. If labor does not start, the drug is repeated after twenty-four hours.

MORTALITY

The mortality is uncorrected. It is to be remembered that none of the women was normal and all of them were colored charity patients. The mortality was 1.9 per cent. A brief abstract of the 6 deaths is as follows: (1) Hypertensive heart disease, chronic nephritis and uremia. Attempted induction at six months. Died before labor started. The induction was probably bad judgment. (2) Eclampsia, aged 17, twin pregnancy. Died before labor started. (3) Chronic nephritis and uremia. Induction at five months. (4) Eclampsia and abruptio placentae, seven months, spontaneous delivery. (5) Eclampsia, died before labor started. (6) Eclampsia, spontaneous delivery.

PARITY

The pregnancy was the first for 124 of the women; 198 were multiparas.

AGE

Distribution as to age is shown in Table I. It is generally recognized that pre-eclampsia and eclampsia have a high incidence in young women. However, it was rather startling that the study revealed so many young women with chronic vascular disease. The incidence of this disease in colored women is probably much higher than in white women. Only 45 per cent of the women were older than 25 years.

TABLE I. AGE DISTRIBUTION

AGE	CASES		AGE	CASES		AGE	CASES
13	2		24	11		35	6
14	5		25	13		36	11
15	7		26	11		37	5
16	14		27	18		38	5
17	21		28	11		39	3
18	23		29	14		40	5
19	20		30	11		41	1
20	17		31	6		42	3
21	10		32	9		43	2
22	15		33	13		44	1
23	20		34	9			

INDICATIONS

Hypertensions of one sort or another were the primary reasons for the inductions in 87 per cent of the women. All indications are shown in Table II. It will be seen that 107 of the inductions were done because of chronic vascular disease. Since this work started we have become a bit more conservative as regards essential hypertension. When the diagnosis is made in early pregnancy and the hypertension is severe, we think the pregnancy should be terminated and the woman sterilized. When the diagnosis is made at the fifth or sixth month and there are no evidences of heart failure, kidney damage, or superimposed true toxemia, we wait until we are sure of viability, induce labor and sterilize later.

It seems worthy of mention that in eclampsia every attempt is made to control the convulsions before the induction is started.

TABLE II. COMPLICATIONS

305 None
  8 Postpartum hemorrhage
  2 Prolapsed cord
  1 Prolapsed arm
  2 Retention piece of placenta
  1 Placenta previa
  2 Abruptio placentae
  1 Dystocia

METHOD OF INDUCTION

Rupture of the membranes was the basic procedure used. One medical induction is included through error.

THE LATENT PERIOD

The latent period was less than twenty-four hours in 86 per cent of the labors. Inductions with such latent periods rarely occasion anxiety. It is the approximate 14 per cent with more or less long latent periods that cause us concern. When one decides to induce labor by rupture of the membranes, all bridges are burned; one's steps cannot be retraced. If the latent period remains fever free, its length causes little worry. As will be discussed under morbidity, only 47 women in the series had as much as a single rise of temperature to 100.6° F. It is believed that the routine instillation of metaphen into the vagina was in large measure, responsible for the low incidence of fever. When we figure that 51 per cent of the women had reached only the eighth month of gestation or less, it is not surprising that there were so many long latent periods. A woman at term is far more likely to have a shorter latent period than one at eight months. However, there are surprises either way.

MORBIDITY

The patient whose temperature reached 100.6° F., one or more times after the membranes were ruptured, was considered morbid. There were 47 such women, or 14.6 per cent. Twelve occurred during the latent period and/or in labor, 7 during labor and the puerperium, and 28 during the puerperium. Most were transient rises because a study of each record enabled us to classify them as follows: Sepsis 2, mild sepsis 5, and respiratory infection 1.

As has been mentioned, we believe that routine vaginal instillations of antiseptic solutions contributed materially to this low morbidity.

COMPLICATIONS

There were no complications in 94.7 per cent of the labors (Table II). It does not seem probable that all of the complications listed can be attributed to the inductions; however, no corrections of any sort were made.

FETAL MORTALITY

We have included in fetal mortality those babies that were stillborn as well as those who were born alive but died in the nursery. Unquestionably most of these term deaths were not caused by the inductions, but by the conditions indicating induction. However, it seems best not to attempt any corrections. The mortality rate for term babies was 4.9 per cent.

The uncorrected premature fetal mortality was 23.4 per cent. Any criticisms of this high figure should be directed against the wisdom of the judgment ordering the inductions rather than at the method.

Our clinic has long been giving maternal life every advantage over problematic fetal life.

TABLE III. CONDITION OF BABY

Term (2,500 gm. and over)		
Alive		174
Dead	4.9 per cent	9
Premature (1,500-2,500 gm.)		
Alive		90
Dead	24.4 per cent	27
Abortion (under 1,500 gm.)		
Alive		2
Dead		22

LENGTH OF LABOR

That induction of labor by rupture of the membranes does not prolong labor seems to be shown by the fact that 87 per cent of the labors were twenty-four hours or less. As a rule, the long labors were the ones with long, irregular and ineffectual first stages. I did not see most of the women during labor and therefore cannot say accurately just how long the labor actually lasted.

METHOD OF DELIVERY

Three hundred and seven women delivered spontaneously. The operative incidence was 4.6 per cent. There were 12 breech presentations in the series. Ten of these patients delivered spontaneously.

PERIOD OF GESTATION

In general it is true that the nearer the woman is to term the shorter the latent period. However, there are so many exceptions both ways that a seven or eight months' pregnancy should not be a contraindication for induction by rupture of the membranes.

EYE GROUND EXAMINATION

Ophthalmoscopic study was done 231 times. Positive pathology was determined in 82.7 per cent of the women studied. That practically all of the examinations were done by one man increases the value of the results. Hallum and Bartholomew have done much work along this line in our clinic, and I am quoting at length from their report because of the great practical importance of the procedure:

"The necessity for induction of labor arises most frequently in connection with toxemia of pregnancy. It is therefore important to know if the toxemia is of the more urgent preeclamptic type and, if so, how long one may safely temporize before terminating the pregnancy.

"Without minimizing the importance of the blood pressure, urine examinations or clinical symptoms, the ophthalmoscopic findings should be considered of great value in answering the above questions.

"If hypertension has existed since the early months of pregnancy, the condition is probably that of chronic vascular disease. The arteries appear pale, the light reflex or arterial stripe is definitely increased, and there is a disturbance in arterio-venous ratio from a normal of 2 to 3 up to 1 to 2, 3 or 4. Slight irregularities in caliber may be found but arterial spasms are rarely seen. Due to sclerosis of the arterial wall there is a distinct arterio-venous compression where an artery crosses a vein, with dilation of the vein, distal to the compression. If one sees yellow-white exudates or cotton-wool patches, there is probably an associated chronic nephritis.

"If hypertension arises late in pregnancy, the condition is usually one of true toxemia of pregnancy, which may progress to preeclampsia or eclampsia. The A.V. ratio is normal and there is no increase in light reflex, and no A.V. compression. Within a radius of two or three disc diameters of the disc, one may find one or more sharply localized arterial spasms. With further increase in toxemia, the spasms become spindle-shaped and finally lengthen until the whole artery becomes constricted. At this stage it may simulate chronic vascular disease except for the associated severe toxic symptoms and findings. Marked edema of the retina and hemorrhages may be seen in the preeclamptic or eclamptic stage."

COMMENT

It is probably true that we are more justified in sanely temporizing with intelligent private patients on a good economic level. However, I think this is often overdone. I still think that too great value is placed upon problematic fetal life and the mother subjected to unwarranted risks in its name. Often, too, is this not the excuse for lacking the courage of our convictions and the will to proceed with a disagreeable task?

In the light of our present knowledge I do not believe that we can tell just what is the influence of conservative treatment of the true toxemias upon subsequent hypertension and chronic nephritis. It is perhaps greater than we realize at the present time. Pregnant hypertensive women with one or more living children deserve humane as well as religious consideration.

In conclusion, I believe that I am justified in making one positive statement. The greatest factor in differentiating the various hypertensions of pregnancy is a prolonged period of observation.

THE RELATIONSHIP OF THE TIME OF LIGATION OF THE CORD TO THE RED BLOOD COUNT OF THE INFANT*

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TARNIER taught that to tie the cord at once deprived the infant of the blood that was left in the engorged placenta, which with more patience would have returned to the body of the infant.

To give some experimental support to his master's teaching, Budin measured the blood that flowed out of the umbilical vessels when the cord was cut at varying intervals of time. In 32 cases the cord was not tied until pulsation had ceased. The umbilical vessels pulsated from one-half to fifteen minutes, with an average time of two and one-fourth minutes. The average amount of blood that flowed out of the cord was 11.2 c.c. In 30 cases in which the cord was ligated at once the average amount of blood collected was 98.4 c.c. In 13 cases in which there was a delay in tying the cord of from one and three-fourths to seven minutes, but in which the cord was still pulsating, the average amount of blood from the cord was 41.46 c.c. Schückling, writing two years later (1877), called this blood ''reserve blood.'' It is used, he said, to fill the pulmonary vessels when they expand. He demonstrated an increase in the babies' weight of from 30 to 110 gm. when the umbilical cord is not clamped. The babies whose cords were tied immediately had a more rapid pulse and gained weight more slowly. Whereas those whose cords were tied late had a slower pulse and regained their birth weight in four to six days. The latter group had no jaundice. This is at variance with the only recent article we have seen on the subject, Franklin noting a higher percentage of jaundice in the babies whose cords were tied late. Hazelhorst not only weighed the babies before and after the cord stopped pulsating, but recorded the weight change graphically by attaching a writing point to the beam of the balance. In some cases where there were strong pulsations of the umbilical vessels there was a loss in weight at first, but an ultimate gain as the vessels ceased pulsating. The average gain in 20 cases was 114 gm. The greatest gain took place in the first few minutes. Uterine contractions caused a gain in weight of the baby.

For a number of years one of us has noticed a marked variation in the number of red blood cells of the newborn infant. Apparently neither the method of delivery nor the type of anesthetic had anything to do with it. The present study was undertaken in hopes of throwing some light on this subject. We repeated Schückling's experiment of weighing the baby immediately and after the cord ceased pulsating. It was easy to demonstrate a definite gain in weight when the cord ceased to pulsate.

In upwards of 400 unselected cases the umbilical cord was tied at varying intervals from one to fifty minutes. The patients were white private patients. All had sodium amytal scopolamine analgesia and ether anesthesia. It is interesting to note that the cord continued to pulsate longer than in Budin's series where probably no anesthesia was used. In one instance pulsations continued for fifty minutes. The amount of blood that drained out of the placental end of the cord was measured.

A blood count was made by the hospital technician within twenty-four to thirty-six hours. The infant's red blood cells varied from 3,280,000 to 7,120,000. In 59 cases in which the cord had ceased to pulsate before it was tied, the infant's red blood cell count averaged 5,783,400, whereas in 333 cases in which the cord was pulsating when tied the red blood count averaged 5,198,919, a difference of 584,481.

We have plotted 400 cases in relation to the time of tying the cord and the infant's red blood cells in millions. Apparently there is little if any correlation. The coefficient of correlation worked out by Pearson's formula is +0.105 and the probable error is ±0.0329. The correlation is positive but not significant as it is only three times the probable error.

We also have plotted 400 cases in relation to the time of tying the cord and the amount of blood left in the cord and placental vessels. Here too there is apparently little correlation. However, the coefficient is −0.2564. The probable error is ±0.0315. As the coefficient is more than six times the probable error it is significant.

The cases were likewise plotted in relation to the infant's red blood cells in millions and the amount of blood left in the cord vessels in cubic centimeters. Here there is apparently some negative correlation. The coefficient of correlation is −0.36 and the probable error is ±0.0293. The correlation is not great, but as it is more than twelve times the probable error it is significant.

DISCUSSION

There is practically no correlation between the number of minutes that elapse before the cord is ligated and the red blood cell count of the infant. One factor that does not show in these figures is the cessation of pulsation. If a cord be watched immediately after delivery the umbilical vessels can be seen to pulsate strongly throughout their entire length. In a varying length of time the pulsations cease in the more distal part and as this occurs the umbilical vessels collapse. This process of cessation of pulsation and collapse of the vessels proceeds toward the umbilicus until finally there is no pulsation even at the navel. The vessels are then entirely collapsed. If now the cord be tied and cut very little blood will escape from the placental end. The cord may cease pulsating at any time, sometimes even before the baby is born. There may be other factors involved, but certainly the length of time before tying the cord *per se* has no influence on the amount of blood left in the umbilical vessels.

On the other hand there is a significant negative correlation between the amount of blood that is left in the umbilical vessels and the number of red blood cells in the infant's circulation. This is also shown by higher red blood cell count of those infants whose cords were allowed to stop pulsating before they were ligated. Here too there are probably other factors. This factor, however, is significant enough to justify waiting until the cord ceases to pulsate and the umbilical vessels collapse especially in small and premature infants.

CONCLUSIONS

1. The less blood that is left in the umbilical vessels the higher will be the red blood cell count of the infant.

2. If the umbilical vessels are allowed to cease pulsating and collapse before they are ligated, very little blood will drain out of them.

3. In infants whose umbilical vessels are ligated after they have ceased to pulsate, the average red blood cell count is greater by 584,481 than in those whose cords are ligated while still pulsating.

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MEDICAL ARTS BUILDING.

PELVIC INLET VARIATION IN 400 NEGRO WOMEN*

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THE modern classification of the female pelvis which has been developed slowly during the past 100 years has culminated in the work of Caldwell and Moloy[1] and Thoms,[2] and others.

It has been shown that external measurements of the pelvis bear little relation to the internal measurements. The external conjugate, considered to be the most reliable of these, may be very inaccurate as an index to the conjugata vera as shown in a recently examined case of an achondroplastic dwarf whose Baudelocque measurement was 17. The conjugata vera as determined by internal measurement and confirmed by the grid method of roentgen pelvimetry was 6 cm.

In fact, external pelvimetry is of so little value that we believe the time has come when it can be discarded. The estimate of the constitutional type of the patient is of far greater value in prognosis of labor. Women of slender and medium constitutions as a rule do well. Those giving most trouble in labor are the overweight, heavy-featured type, with male distribution of hair. These are inclined toward the Froehlich type, the dystrophia dystocia syndrome described by Horner[3] and, in addition to a tendency to possession of rarer types of pelvis and a predilection for occipitoposterior presentation of the fetal head, have painful but ineffective uterine contractions, possibly associated with hormonal disturbances. Of all methods of study of the obstetric pelvis short of roentgenography, the most valuable is estimation of the conjugata vera by subtracting 1½ to 2 cm. from the measured conjugata diagonalis. Criticism has been made that the promontory cannot be palpated in all patients. When that occurs the diameter is usually large enough. In all cases of contraction in which the conjugata vera was 9 cm. or less, we have been able to estimate it within 0.5 to 1 cm. as checked by the x-ray "grid" method. Palpation of the contour of the ischial spines and the subpubic angle gives a fairly good estimate of the outlet.

This study of 400 negro female pelves, made entirely upon the dimensions and outline of the superior strait, was associated with the use of a device previously described[4] for simplifying Thoms' method of roentgenpelvimetry with which we routinely use an 8 by 10 inch film. Most of these patients were not pregnant. Many were pregnant and some in the first stage of labor. They were studied as far as possible in conformity with published studies on series of white women. As a rule the contours of the inlet allow fairly definite classification as to the four

GYNECOID TYPE 60 %

ANTHROPOID TYPE 31 %

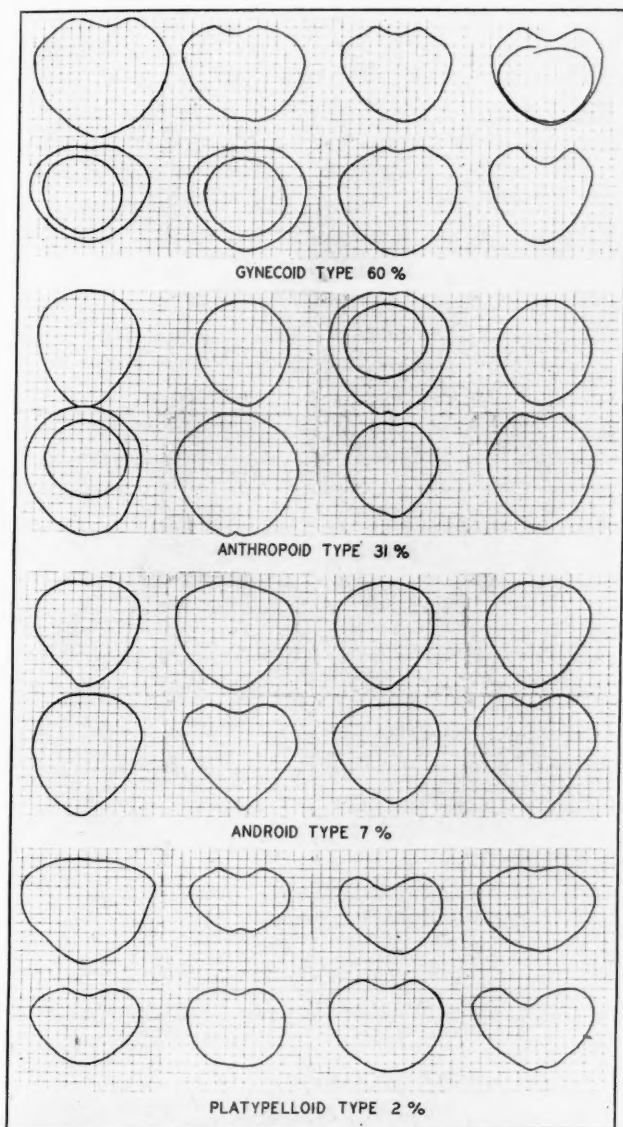ANDROID TYPE 7 %

PLATYPELLOID TYPE 2 %

Fig. 1.—Chart showing actual outlines, drawn to centimeter scale, of individual pelvic inlets from the group of 400 negro female pelves. The incidence of each of the 4 types is stated.

groups of Caldwell, Moloy and D'Esopo,[5] gynecoid (female type), an-
thropoid (ape or fetal type), android (male type) and platypelloid
(flat pelvis type). However, many cases overlap, so that characteristics
of two or possibly more of the groups occur in the same pelvis. Cald-
well and others have taken care of this by subgroups which they illus-
trate. In order to correlate this study in regard to colored women with
theirs in white women, we have consulted their drawings of the various
subtypes and have taken the liberty to group them all under the four
main heads. In their 215 white women then, what we would classify as
gynecoid occurred in 58.5 per cent, anthropoid 18.1 per cent, android
22.2 per cent, and platypelloid 0.9 per cent.

Our classification of the negro pelves by the same standards is, gyne-
coid 60.25 per cent, anthropoid 31 per cent, android 6.75 per cent and
platypelloid 2 per cent. In this classification the principal difference
between the two races lay in 80 per cent more anthropoid and more
platypelloid types and less than one-half as many android types in the
negro in comparison with the white women. Table I shows the number
of cases in each group with the different lengths of the conjugata vera.
The majority fall into the group with conjugata vera of 10 to 11 cm.
Thoms has a somewhat similar classification but it seems to exclude the
male type pelvis and is based more on the relation between the antero-
posterior and transverse diameters as revealed by the "grid" method
of roentgen pelvimetry. This work on the negro pelvis however bears
out his contention that the average normal female pelvis is essentially

TABLE I

Gynecoid					
CV in cm.	8½	9	10	11	12
Cases	1	30	111	90	9

Anthropoid					
CV in cm.	9	10	11	12	13
Cases	1	22	64	29	8

Android					
CV in cm.	9	10	11	12	
Cases	3	14	9	1	

Platypelloid					
CV in cm.	6	7	8	9	10
Cases	2	2	1	2	1

TABLE II*

	WHITE 100 NURSE	132 CLINIC	450 CLINIC	107 CHILDREN	400 NEGRO WOMEN TORPIN
Dolichopellic	37	14.6	15.5	57.9	9.25
Mesatipellic	46	43.9	45.1	33.6	36.50
Brachypellic	17	34.1	34.5	8.3	49.75
Platypellic	0	8.3	4.9	0.0	4.50

*NOTE: Thoms' chart of classification of white female pelves are shown in the
first four columns. The fifth column incorporates the 400 negro female pelves of this
study grouped according to Thoms' classification.

round, inasmuch as 64 per cent of them appeared to be essentially round to the casual observer and, in fact, the radii in any such case varied no more than ½ cm. in length. Table II compares the group with that of Thoms.

Thoms records the delivery of the 600 white patients studied. There were 15 cesarean sections, 76 low forceps, 18 midforceps, and 4 version and extraction operations performed. While we have no record on these particular 400 colored patients, our operative incidence on this class of patients is about as follows: Cesarean operation once in about 200 cases and forceps, low and mid, about 2½ per hundred deliveries. McCord (personal communication) has even a lower operative incidence. "In 600 consecutive deliveries, all colored patients, there were 2 cesarean, 9 low forceps and 1 midforceps operation."
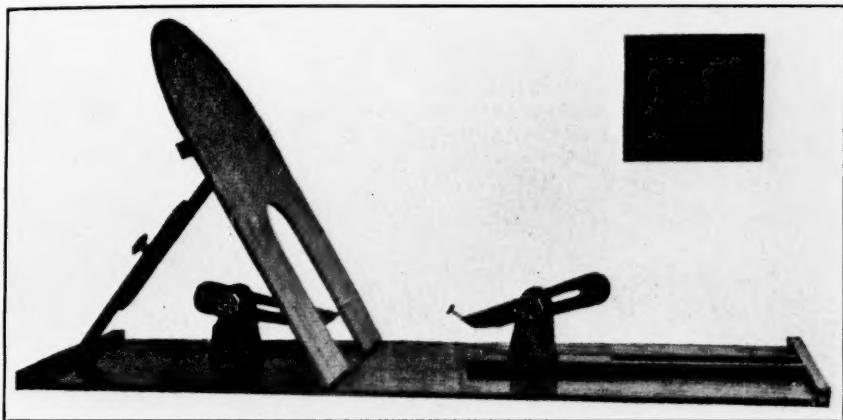

Fig. 2.

It may be added that in the series of 400 pelves reviewed, there were 3 cases which were sent from other clinics merely because of the extreme degree of contraction. One of these was a dwarf whose conjugata vera was 6 cm. This unduly increases our platypelloid group.

In this study most of the films were quite readily classified into the four groups, gynecoid, anthropoid, android, and platypelloid, but there was one feature of the superior strait not discussed by recent writers and that is a forward placed promontory jutting out into the posterior aspect of the superior strait. No note was made of this unless it extended 1 cm. or more. This occurred in 10 per cent of the series, 9½ per cent of the gynecoid, 7 per cent of the anthropoid, 15 per cent of the android, and 62 per cent of the platypelloid. Consequently this is an important factor in the estimation of each patient's ability to deliver, especially when the type of the pelvis is platypelloid, android or gynecoid. It was the determining factor in two recent cesarean operations after prolonged test of labor in gynecoid pelves of small dimensions,

with large fetuses. The forward jutting promontory was noted in the film of the superior strait and was demonstrated at the operation in each case.

SUMMARY

1. Study of the superior strait in 400 negro female pelves by Thoms' grid method revealed more anthropoid and less android types of pelves than occur in the white patients as studied by Caldwell and others.

2. A device is illustrated (Fig. 2) for simplifying Thoms' grid method so that the superior strait may be viewed and measured from an 8 by 10 inch film and a technician may complete the procedure in ten minutes.

3. The inlet to the majority of negro female pelves is essentially round in agreement with Thoms' findings in white women.

4. The operative incidence of the negro women may be less than in the whites partially because of less occurrence of android type of pelves.

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ENDOMETRIOSIS OF ROUND LIGAMENT WITH REPORT OF CASE*

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ENDOMETRIOSIS of the round ligament is a rather rare condition and that is the reason for the report of this case.

Mrs. T. J., aged 29 years, weight 126 pounds, reported to me on Aug. 3, 1938, complaining of pain in right groin. The pain had been present for last nine years; for the past six years, she had noticed a small nodule in right inguinal region, which was painful; on pressure, the pain radiated into the lower right quadrant; the pain was worse at night and frequently the patient could not sleep due to pain in the right inguinal region. The symptoms were increased during the menstrual period.

This patient had been married ten years. There had been no pregnancies, although no contraceptives had been used. Mother died at the age of 58 years of carcinoma of fundus of uterus. Father died at the age of 63 years of angina pectoris.

In 1931, seven days before menstrual period was due, patient had an attack of lower right quadrant pain. She had an appendectomy done at midnight and was told by the surgeon that her appendix was not bad. Her convalescence from the appendectomy was normal. She remained in the hospital for ten days.

This patient had had the usual childhood diseases, no serious illnesses. Menses began at 11 years, regular every 28 days, lasting 5 days. No pain except in right inguinal region. The Wassermann reaction was negative, hemoglobin, 85; red blood count, 4,830,000; white blood count, 6800; leucocytes, 68; lymphocytes, 26; monocytes, 4, and eosinophiles, 2; urine, negative.

General physical examination negative except for a small tender mass in right inguinal region about 3.5 by 2.5 cm in size. This mass was lying over the pubic bone and apparently was attached to it. X-ray examination revealed no bony pathology.

On return visit, the small mass was manipulated and the patient complained of severe pain. After a week, the pain gradually subsided, although the mass was still tender, but on subsequent visit the mass was found to be mobile.

Pelvic examination was negative.

On Aug. 28, 1938, a right inguinal incision was made extending from the canal of Nuck to symphysis. The nodule was explored and removed and the mass was found to be a continuation of round ligament. The ligament was removed high in the canal and transfixed.

The following is the pathologic report by Dr. Kenneth M. Lynch: ''Received a somewhat rectangular piece of tissue measuring approximately 3.5 by 1 cm. in diameter. The surface is covered by a rough, thin, whitish gray membrane. Section reveals a white fibrouslike center. Also received a small irregular sheetlike piece of tissue measuring 1 cm. in greater diameter and containing 2 catgut sutures.

''Two sections of tissue, one containing muscle and showing serous membrane covering on one side. The other is of more dense connective tissue and containing islands of cellular stroma resembling that of the endometrium, enclosing channels, lined by columnar ciliated type epithelium, containing blood and granular debris.''

Diagnosis: *Endometriosis of round ligament.*

CURRENT VIEWS ON THE CAUSATION OF MENSTRUATION*

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THE modern phase of studies on the menstrual cycle began seventeen years ago when Corner began observing the menstrual cycle of the monkey. Following the lead of Corner, Edgar Allen used the newly discovered estrogenic hormone on ovariectomized monkeys and first stated his belief that menstruation was caused by withdrawal of estrogen, which has been elsewhere called the estrin deprivation theory.

A brief recapitulation of the stages which permit our present interpretation of the role of the sex hormones is necessary, although the details are familiar to many. The first experimental observations were those of Allen, which were the basis for the estrin withdrawal theory which he and many other observers still maintain. There is no doubt that withdrawal or reduction of the estrogen level by any means results in typical uterine bleeding. The high incidence of anovulatory menstrual cycles in the monkey, especially those in captivity, makes this animal an excellent form for those who would elaborate and justify this theory. So in all of these experiments, the bleeding which followed estrogen withdrawal is a result of the breakdown of a proliferative endometrium. This phenomenon of uterine bleeding after withdrawal of estrogen can best be summarized graphically (Fig. 1).

The bleeding threshold to estrogen withdrawal has been approximated by Zuckerman[1] from a large series of observations. He determined that the amount of oil used as a vehicle for injection is of no significance, and that dosage per day, whether 0.03 mg., 0.1 mg. or 1.0 mg., made little difference in the latent interval between withdrawal of the hormone and bleeding. Zuckerman[2] injected spayed animals with a standard amount of estrogen which, in individual cases, ranged from 400 I.U. daily to 5000 I.U. daily for fourteen days. When this dose was reduced in varying amounts and percentages, a bleeding threshold to estrogen was determined. Thus, the dosage to which such pretreatments could be reduced without permitting bleeding was found to be not below 250 I.U. daily. Below this level, that is, between 150 I.U. and 250 I.U., lies the threshold for bleeding in which some animals will bleed. Zuckerman suggests that 200 I.U. may be taken as a uterine threshold for most monkeys.

The other point of interest here is that the percentage of reduction which is made in lowering the dose is of no significance. That is, the treatment may be at 400 I.U. per day or 5,000 I.U. per day. Uterine

bleeding will occur only if the estrogen level is reduced to the threshold zone, approximately 200 I.U. for the rhesus monkey. This would signify a drop of 50 per cent or of 4 per cent but bleeding occurs only within the threshold zone.

The course of action of a single injection of various estrogens was followed in a small series of animals (Engle and Crafts[3]).
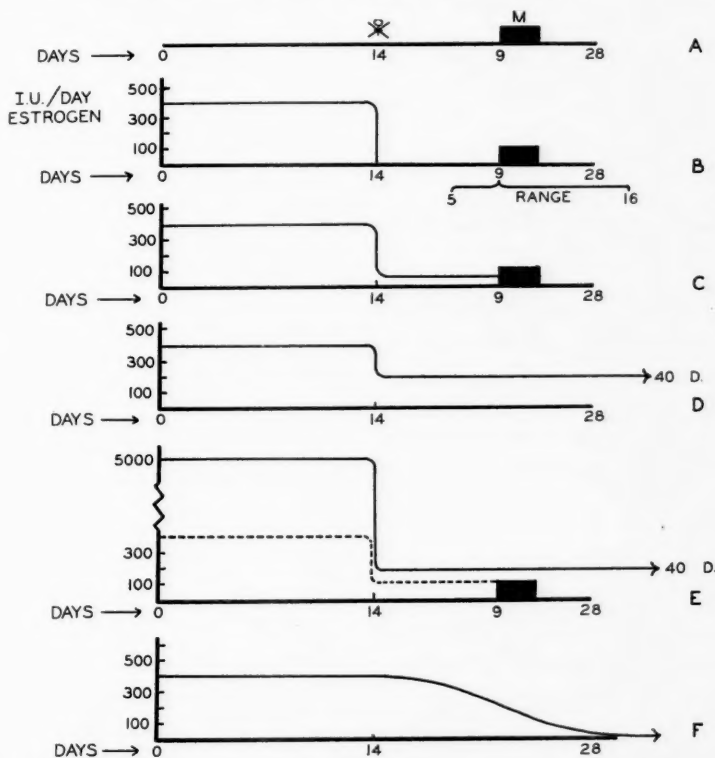

Fig. 1.—Estrogen-threshold and uterine bleeding, showing observations made over a period of years by a number of investigators, and which have become common experience among workers in the field of experimental menstruation in monkeys. *A*, Estrogen withdrawal by means of castration only in adolescent or adult animal, not in infants or juveniles. *B*, Cessation of injections of estrogen. *C*, Bleeding will occur if the amount of available estrogen is reduced below the endometrial threshold. *D*, Bleeding can be prevented for variable periods of time even though the amount is reduced, provided it is above the threshold level. *E*, The quantity of estrogen originally given is not a factor, neither is the percentage of reduction of estrogen, nor is the amount of oil used as a vehicle important, provided that the endometrial threshold is exceeded (Zuckerman). *F*, Involution of the endometrium may occur without bleeding by the gradual reduction of estrogen (Hisaw).

A single injection in an area where slow absorption of the oily vehicle might be expected showed that the bleeding would appear on the thirtieth to the seventieth day after the single injection (Fig. 2).

An attempt has been made to present the evidence to date regarding the conditions under which the withdrawal of estrogenic hormones is followed by bleeding. It is, however, obvious that, interesting as the observations may be, they do not explain the role of estrogens in the ovulatory menstruation of the normal adult woman.

In earlier work we[4] showed that the bleeding of estrogen deprivation did not occur if the estrogen were replaced by progesterone. After a course of progesterone, bleeding always occurred after the withdrawal of progesterone.

The same series of experiments[5] also demonstrated that this bleeding was not prevented by following the progestin by doses of estrogen several times larger than would effectively prevent bleeding without the progesterone treatment. These observations were confirmed by Hisaw and his associates, and by Corner on the monkey, and by Kaufman and many others for women.
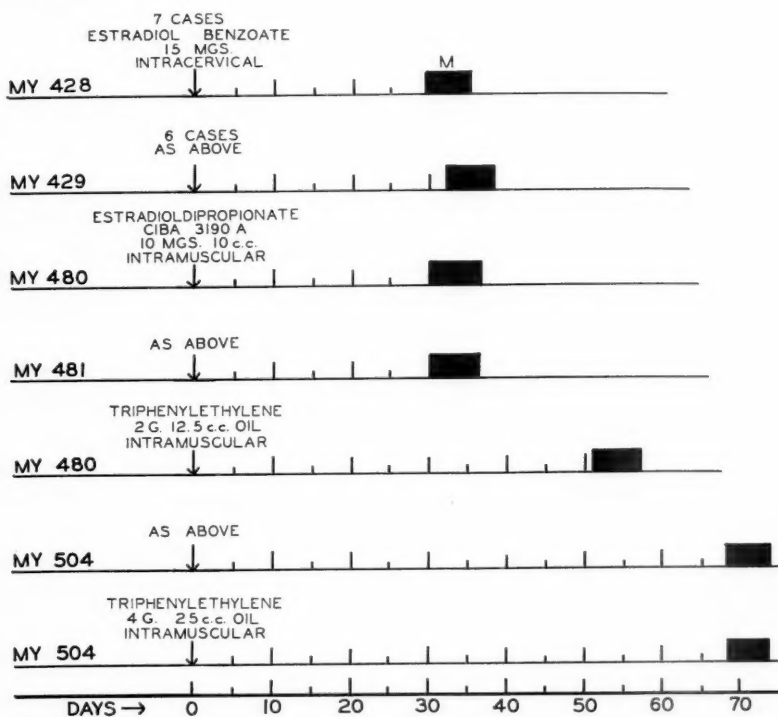

Fig. 2.—Graph showing latent period for uterine bleeding in days after a single injection of various estrogens.

These experiments on monkeys and women merely established that which was already believed from clinical and pathologic experience, viz., that the histologic sequences of the menstrual cycle were induced by the ovarian hormones, and that menstrual bleeding from a progravid endometrium followed cessation of progesterone action on the endometrium.

The character and duration of the bleeding resulting from withdrawal of either hormone are the same. The time interval between hormone withdrawal and bleeding, however, is characteristic for each hormone.[6] The time of onset of bleeding after estrogen withdrawal is 9.2 days, with a range of five to sixteen days. After cessation of progesterone treatment, however, bleeding occurs on an average of 2.9 days, with a range of two

to four days. Thus, while the latent period before bleeding after estrogen withdrawal is quite long, and the variability great, it is very brief and constant after progesterone withdrawal (Fig. 3).

These observations have been made by given periods of injection with estrogen or with progesterone. In attempting to reproduce the hormonal regulation of the human menstrual cycle, however, it could not be
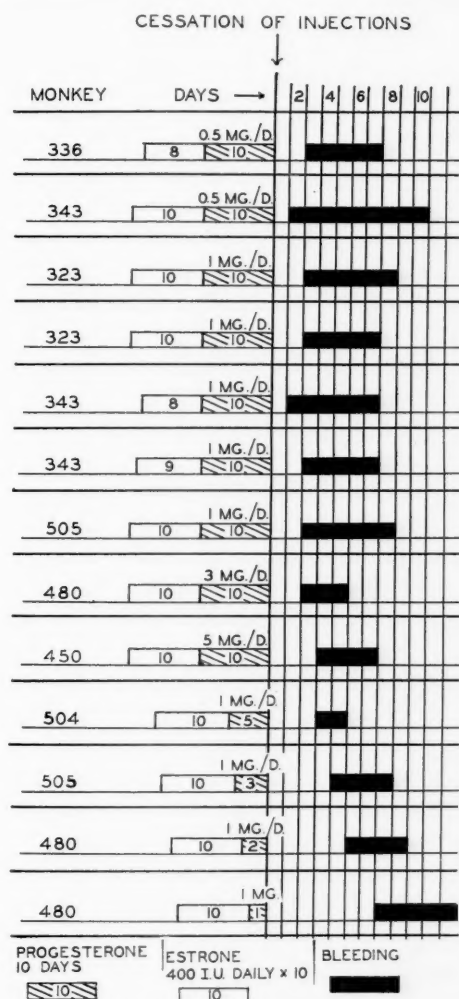
Fig. 3.—Graph showing the latent period for uterine bleeding in days after progesterone withdrawal.

thought that there was any such sharply demarked line of separation between the two. That is, no one could consider that the action of estrogen stopped suddenly at the hour of ovulation. Indeed, all data available indicate that estrogen was present, and was probably continually being produced by the follicles or the corpora lutea during the entire cycle. Experiments of our own,[8] as well as those of Hisaw and Greep,[9] indicated

that estrogen and progesterone were not antagonistic in their action on the monkey endometrium, but were essentially synergistic.

In these observations, we were interested in structural changes of the endometrium, and presented some evidence that estrogen and progesterone might act together in preparing a progravid endometrium. Similar studies on the human being have not been reported, but these experiments were designed to repeat the conditions of hormone balance and action, believed to be true in the human menstrual cycle.

Attempts to analyze the endocrine factors involved in menstruation have involved the adrenals, thyroids, and the anterior and posterior pituitary glands. All attempts to demonstrate direct participation of these hormones in the bleeding process have been negative.

The anterior hypophysis participates indirectly in the menstrual cycle, but the work of Philip Smith shows so clearly that the bleeding response to estrogens and to progesterone is not greatly changed in completely hypophysectomized monkeys. Direct action of the pressor principle of the posterior hypophysis also appears to be without effect on the bleeding response.

Thus, the experimental trend has returned to the task of determining the respective roles of estrogens and progesterone withdrawal in the bleeding response.

There is now no controversy over the relationship of progesterone to the latter half of natural or experimental cycles. The bleeding of estrogen withdrawal is invariably prevented if progesterone is administered. In normal nonovulatory or ovulatory cycles, progesterone administration will inhibit menstruation for the duration of the treatment. Estrogen administered in the latter half of an ovulatory cycle in monkeys or woman has no effect on the time of appearance of the menses. Bleeding follows cessation of progesterone administration, even though very large quantities of estrogens are given. General agreement exists among the workers with monkeys as to the validity of these facts. Recognizing these experimentally observed facts on the immediate role of progesterone in inhibiting bleeding, Corner[10] has made "the assumption that progestin acts to prevent estrin from protecting the endometrium against bleeding."

In his experiments where estrogen and progesterone were given concurrently, it requires much more estrogen than the combined "bleeding prevention" values of the two substances to inhibit bleeding after the cessation of the two.

Corner[10] found that 125 I.U. of estrogen per day for ten days would be followed by bleeding on withdrawal. The threshold value of progesterone for bleeding inhibition was about 0.5 mg. By combining the two substances he obtained a "bleeding prevention" value of 325 to 425 I.U. of estrogen. However, after cessation of these combined injections he found that the bleeding prevention value needed was about 750 units. From these data Corner derives his thesis that progesterone suppresses the menstrual inhibiting value of the estrogen. He believes that the "significant action of the progestin has been to create, by depressing the action of estrin, a state equivalent to estrin deprivation."

Testosterone propionate (perandren, Ciba) will prevent the bleeding of estrogen withdrawal in monkeys as effectively as progesterone.[11] After the usual ten-day treatment with an estrogen, 5 mg. of testosterone propionate will prevent the bleeding of estrogen withdrawal. Upon cessation of the testosterone, a latent period typical of estrogen withdrawal occurs (eight to ten days). However, after a progestational endometrium is established, dosages of 5 mg. and 10 mg. do not prevent bleeding nor change the time of the latent interval. Dosages of 25 mg. per day do effectively inhibit the bleeding (Fig. 4).
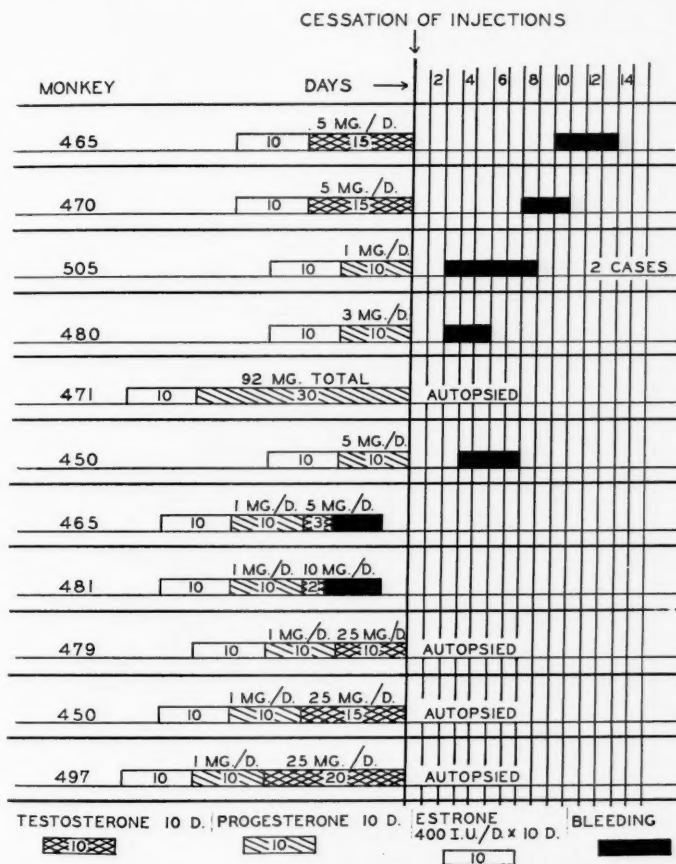
Fig. 4.—Graph showing the latent period for bleeding after testosterone treatment, and its inhibition by progesterone.

The endometrium of ovariectomized monkeys after testosterone injections which follow estrogen is clearly proliferative. That is, if an endometrium is prepared by estrogen, the subsequent treatment with testosterone maintains the histologic character of the proliferative (estrinized) endometrium. When estrogen is followed by progesterone and a secretory endometrium is formed, then adequate dosages of testosterone propionate continue to maintain the high secretory condition developed by

the progesterone, even for twenty days, without bleeding or involution or loss of the secretory character. These experiments are not comparable to the reports on suppression of menstruation in woman with intact ovaries.

In reporting these experiments no explanation is offered as to the physiologic or chemical factors involved in these two diverse effects obtained with the same chemical agent.

In an ovariectomized monkey which has been permitted to bleed, the endometrium after regeneration is the usual thin, sparsely glandular endometrium of castrate atrophy. In such an animal 25 mg. of testosterone daily will cause considerable growth of the endometrium with a high columnar epithelium, but rather dense stroma. The histologic effect of testosterone alone does not completely develop the proliferative phase induced by an estrogen only.

When testosterone is withdrawn, a long latent period of fifteen to twenty-five days occurs before bleeding, which equals or exceeds the longest period of latency obtained with estrogen withdrawal.

Regeneration of the endometrium of an ovariectomized monkey after bleeding may be caused by crude progestin only.[12] Such a degree of endometrial growth as Hisaw reported has not been produced by us with crystalline progesterone (proluton, Schering). Covering of the denuded surface of the endometrium will, of course, occur in the absence of the ovaries or any hormone administration.

Though there is an endometrial growth and proliferation, uterine bleeding has not occurred after the progesterone withdrawal. Dosages up to 5 mg. of progesterone per day, with no pretreatment with estrogen, cause slight endometrial growth, but bleeding does not occur after cessation of such treatment. (Table I.) Zuckerman[13] reported no bleeding after fourteen days' treatment with 2 mg. of progesterone daily.

TABLE I. No Bleeding After Progesterone Only

MONKEY	DAYS SINCE LMP*	PROGESTERONE DAILY MG.	NUMBER OF DAYS INJECTION	OBSERVED AFTER LAST INJECTION	REMARKS
462	10	2½	14	No bleeding in 24 days	
462	--	5	14 Biopsy day 15	No bleeding in 20 days	Microscopic R.B.C. day 3 after biopsy
505	14	5	10	No bleeding in 29 days	
480	5	1	14	No bleeding in 24 days	

*LMP, Last menstrual period.

In summarizing the points discussed, we may accept the following as valid: (1) The anterior hypophysis or any other single endocrine gland is not directly or actively responsible for the initiation of the menstrual flow. Such reaction follows inactivity or cessation of the ovarian hormones. (2) Withdrawal of either estrogen, progesterone after estrogen, or testosterone results in uterine bleeding. (3) Either testosterone or progesterone will prevent the bleeding of estrogen withdrawal. ''Proges-

tin acts to prevent estrin from protecting the endometrium against bleeding."[10] (4) The length of the latent period between the withdrawal of estrogen and the withdrawal of progesterone is significantly and constantly different.

The endocrine balance in the normal menstrual cycle seems to be quite well established. The action of estrogens alone during the proliferative phase, and the development of the progravid or secretory phase through the combined action of estrogen and progesterone appear to be valid. The term "progravid" has been used to designate the histologic stage of endometrial development from the time shortly after ovulation to the cessation of active production of progesterone by the corpus luteum. All indications are that the last phase is a period of forty-eight hours or less which is the true premenstrual stage. It is at this stage of the cycle that attention must be focused to discover the factors which cause the hemorrhage and tissue fragmentation characteristic of menstruation (Fig. 5).

Concomitant with the disappearance of progesterone, either in the artificial experimental cycle or in the normal cycle, several other phenomena have been clearly described by Bartelmez.[16]
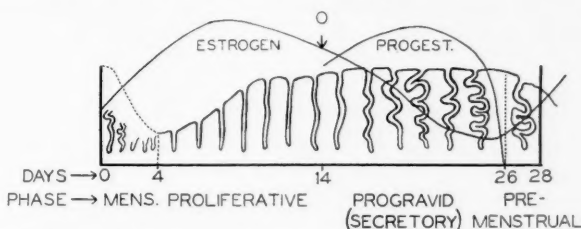

Fig. 5.—Graph of the stages of the endometrial cycle, indicating a possible hormonal balance effecting endometrial change and menstruation of hormone withdrawal.

The coiled endometrial arteries constrict at the base and the stroma of the endometrium becomes dehydrated. The process of dehydration is not understood but the tissue shrinks markedly. The arteriolar flow is supposed to be scanty, the pressure reduced. A peripheral ischemia ensues. This ischemia is the terminal result of the alternating "blush and blanch" arteriolar phenomena which Markee has observed in the ocular endometrial grafts. According to Markee (quoted by Bartelmez), the terminal ischemia lasts for from four to twenty-four hours. After this, subepithelial hematomas appear, followed by their coalescence into lacunae, which begin to bleed into the lumen. Very little tissue is lost during the first twelve hours of the hemorrhage.

It is obvious that the initiation of menstruation is caused or permitted by the withdrawal of one or more of the hormones discussed. The hormone withdrawal theories must assume that during the interval between withdrawal of the hormone and the actual hemorrhage something happens in the tissue of the endometrium. One of the effects of this something is the constriction of the base of the endometrial coiled arteries, with the resultant ischemia. Another concomitant effect is the apparent dehydration of the stroma. The actual bleeding appears to be a result of these conditions.

The case is certainly more clear because more limited and immediate in the case of progesterone withdrawal. In this instance, both in woman and the monkey, bleeding begins within forty-eight hours after progesterone withdrawal. If, during the progravid phase, progesterone merely prevents the protective function of the estrogen, as Corner suggests, it also circumscribes the action to a period of twenty-four hours.

It appears more reasonable to assume that the withdrawal of either hormone permits conditions to develop within the vascular supply or the tissue of the endometrium which leads to the phenomena of menstrual bleeding. In the case of progesterone, these changes become effective at once; after estrogen withdrawal the effect is not so localized in time, and it slowly becomes effective over a period of many days.

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Brunner, Endre K.: Criteria for Fertile Semen, J. Contraception 4: 77, 1939.

A specimen of fresh semen must be judged by the following four criteria: (1) volume of semen; (2) grade of sperm motility; (3) number of spermatozoa; and (4) percentage of abnormal sperms present.

A *good* specimen is more than 3 c.c. in volume; has 50 per cent or better motility six hours after ejaculation; has 50 millions or more sperm cells per c.c. and a minimum of 300 millions per ejaculate, of which 85 per cent must be oval in form, and not more than 7 per cent tapering.

A *fair* specimen is more than 2 c.c. in volume, has 35 per cent motile cells after six hours. The cell count is more than 20 millions per c.c. and a minimum of 150 million per ejaculate, of which more than 70 per cent are oval and not more than 15 per cent tapering.

Anything below these limits is classified as *poor*.

Judging from some of the exceedingly low values which were capable of procreation, it is impossible to condemn any specimen on a single examination. It seems, however, a fair assumption that for every criterion denoted as ''poor'' there must be at least one in the ''good'' column for the semen to be considered fertile.

HUGO EHRENFEST.

THE EFFECT OF INGESTED ESTRONE (PROGYNON DH) AND PARENTERALLY ADMINISTERED SYNTHETIC PROGESTIN (PROLUTON) UPON THE HUMAN CASTRATE UTERUS

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IN A previous communication,[1] it was demonstrated that an ingested extract of estrin was capable of activating the atrophic endometrium of a human castrate. Since then several additional estrogenic substances have been isolated, and also synthetically prepared.

The present communication concerns itself with the action of dihydroxyestrin (progynon DH), a synthetic estrogenic substance with the formula $C_{19}H_{24}O_2$, on the atrophic endometrium of six human castrates. It also refers to the estrin-progestin (proluton) effect, and the urinary excretion of dihydroxyestrin as a supplementary index of biologic potency.

CASE REPORTS AND EXPERIMENTAL PROCEDURES

CASE 1.—F. L.,* white, female, married, aged 33 years, bilateral salpingo-oophorectomy for cystic ovaries. Menstruation began at 14, was irregular with occasional intervals of from three to six months, always painful and profuse, at times lasting thirty days. There had been 4 full-term pregnancies. The castration syndrome developed six months postoperatively.

A twenty-four-hour urinary specimen assayed for estrogenic activity was negative. One progynon DH tablet containing 1,000 active biologic units† was ingested daily for seven days and complete twenty-four-hour urinary specimens were collected and assayed by the chloroform method of Frank[2] (Fig. 1). Following a fifty-five-day interval, the same medication was repeated three times daily for a period of twenty-eight days. On the twenty-ninth day the endometrial biopsy showed an early follicular phase with congestion (Fig. 2).

After a thirty-day interval, the experiment was repeated with the exception that the same daily intake, 3,000 active biologic units, was continued over a period of sixty days, using approximately twice the total amount given previously. On the sixty-first day scanty tissue was recovered following curettage. Definite diagnosis was impossible although an occasional enlarged tortuous endometrial gland was present.

During the first part of the experiment, the patient described occasional spotty bleeding and during the latter course of medication there was staining for a period of twenty-eight days. There was more definite bleeding resembling menstruation during the last four days.

Following a two-year interval, another experiment was undertaken by using intramuscular injections of 50,000 rat units of progynon B. Five divided doses

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*This castrate was reported upon in a previous communication.

†An active biologic unit is the amount which, when taken orally, will produce approximately the same effect as one rat unit of the injectable preparation administered intramuscularly.

were given over a period of fourteen days, at three-day intervals. This series was
immediately followed by the injection of 50 International Units of proluton (syn-
thetic progestin) in divided doses, within a period of seventeen days. In addition,
two injections of 1,000 rat units of progynon B* were given. Previous to medication
the uterus measured two inches. Biopsy revealed an endometrium of a late follicular
phase, no evidence of any luteal change (Fig. 3). Staining occurred for a period
of six days. The uterus at the time of biopsy measured 2⅛ inches. No staining
thereafter. Hot flushes lasting a few seconds occur on rare occasions. Breast symp-
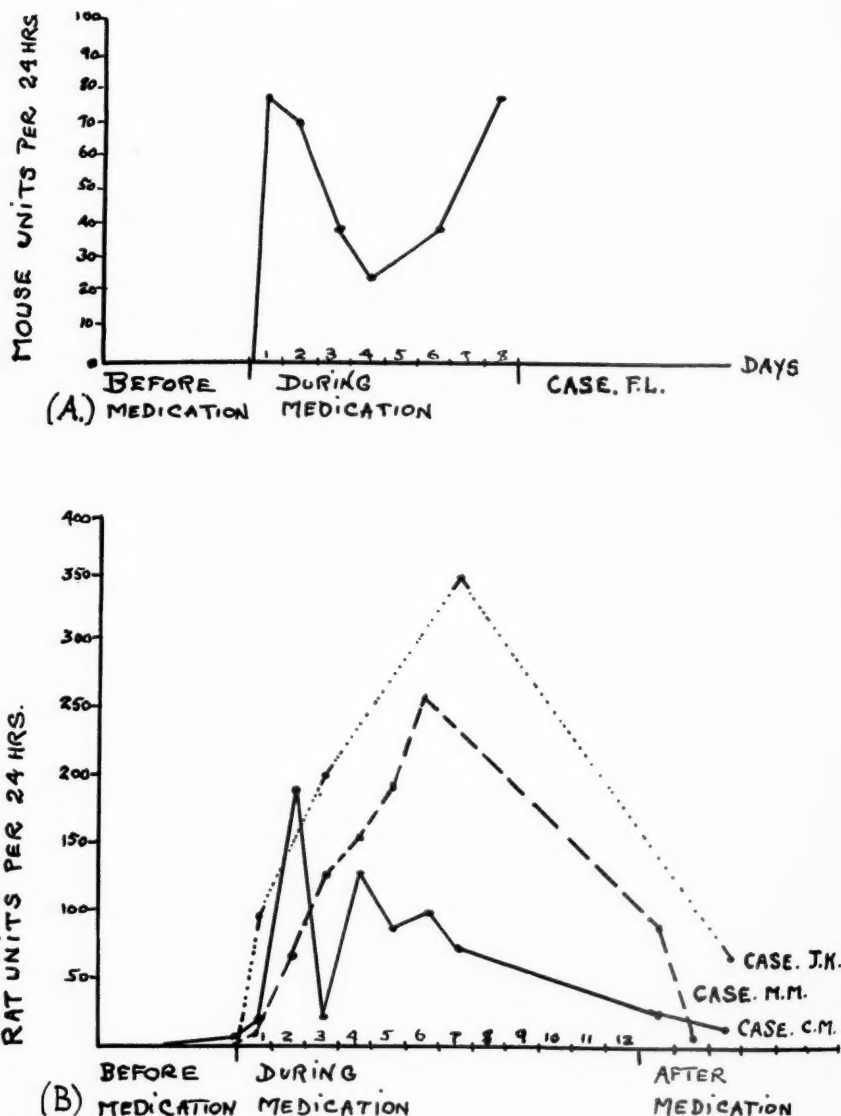toms were present throughout.

Fig. 1.—Assay of daily excretion of estrogenic hormone. A, Original chloroform
method of Frank. B, Modification of chloroform method of Frank.

*The injections of 1000 rat units were administered in error.

CASE 2.—C. M., aged 36 years, single, admitted to the Gynecological-Endocrine Clinic complaining of hot flushes every half hour.   Previous history irrelevant, except for previous operations: Right ovary removed for cystic degeneration nine years previous and the left ovary removed for the same condition six weeks ago.   Menstruation began at the age of 20 years, normal flow with five weeks' intervals which later changed to three weeks.

Bimanual examination revealed a small uterus, anterior in position and freely movable.   The adnexa were not palpable.   The cervix was small, atrophic and pale. The vaginal mucosa was pale and dry.   The uterus measured two inches.   Endometrial biopsy showed an atrophic endometrium in the early follicular phase (Fig.
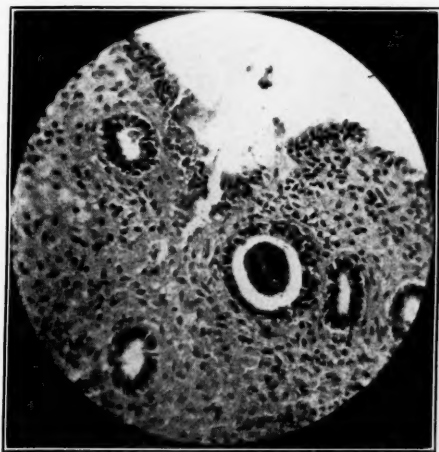

Fig. 2.—Endometrium taken after estrin therapy.   The glands are slightly larger than those of an immediate postmenstrual type.   Stroma is rather loose and very hemorrhagic.   Early follicular phase.

Fig. 3.—Late follicular endometrium with round cell infiltration of the stroma.   No luteal change. (After method of Kaufmann.)

4). A complete twenty-four-hour urinary specimen assayed for estrogenic content, employing a modification[3] of the chloroform technique, was found to contain 4.8 rat units.

For a period of seven days the patient took one tablet (600 active biological units) of progynon DH daily. Complete twenty-four-hour specimens of urine were collected for nine days consecutively, and two additional specimens later on. The last two specimens were collected on the third and fifth days, respectively, after the ingestion of the last tablet. The results appear in Fig. 1.
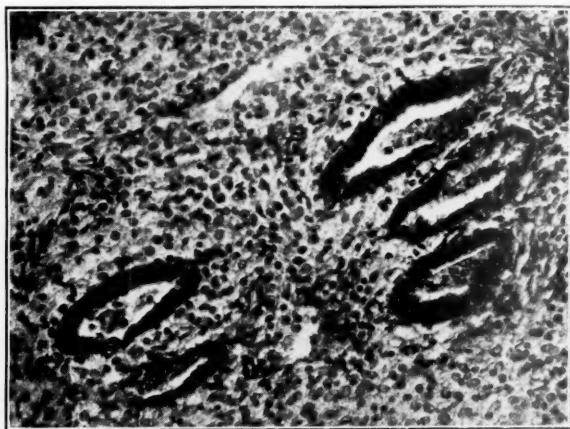
Fig. 4.—Endometrium two months after castration. The glands show beginning atrophy and pycnotic changes. Atrophic endometrium of an early follicular phase.
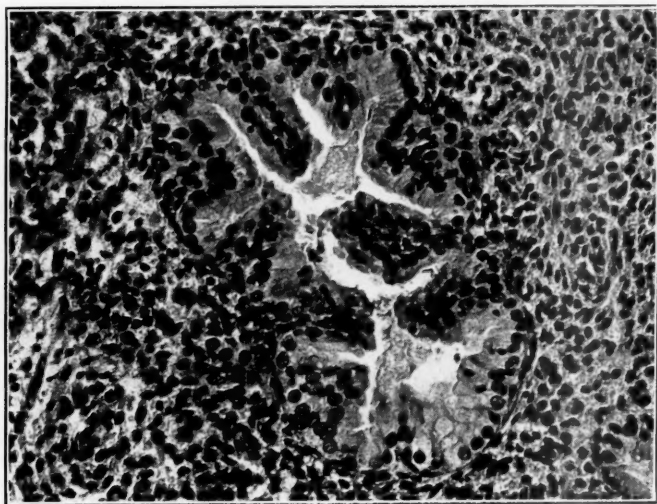
Fig. 5.—Definite luteal change following administration of 144,000 ABU of estrin and 60 International Units of progestin.

One month later for a period of fifteen days, the patient ingested 2,400 units daily of progynon DH. Bleeding occurred for three days during latter part of medication and the patient had the impresion that she was menstruating again. Endometial biopsy showed a normal, mid to late follicular phase. The uterine measurement was 2¼ inches.

Second Experiment.—For a period of thirty days, 2,400 units were ingested daily, and for a following period of ten days, 2 International Units of proluton were injected daily, a total dosage of 20 units. The specimen obtained by biopsy was fixed in absolute alcohol and stained for glycogen with Best's carmine, but there was no evidence of glycogen in any part of the material. Bleeding occurred three days after the biopsy was taken and continued for eight days. During the entire duration of treatment, the patient was completely free from flushes. Seventeen days later the flushes recurred but were not as frequent or severe as prior to medication.

Third Experiment.—For a period of twelve days the patient ingested two tablets (600 units) three times daily and six tablets upon retiring, a total of 86,400 active biologic units. For a succeeding period of twelve days, the patient received one ampoule daily of 5 units of proluton, a total of 60 International Units, plus the continuation of two progynon DH tablets four times daily, an additional amount of 57,600 units. Spotting began the day preceding cessation of medication and bleeding appeared two days later. Endometrial biopsy showed areas of a late follicular phase, while other areas showed definite changes diagnostic of a luteal phase (Fig. 5). The uterine measurement at this time was 2½ inches. The cervix was soft, the vaginal mucosa was of a normal pinkish hue and moist.
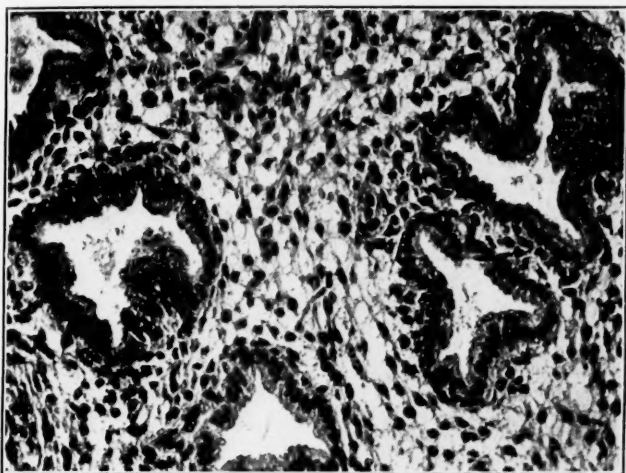
Fig. 6.—Endometrium showing definite luteal change following administration of 144,000 ABU of estrin and 60 International Units of progestin.

CASE 3.—J. K., white, female, married, aged 22 years, was admitted to the Gynecological-Endocrine Clinic complaining of hot flushes and amenorrhea. Both ovaries were removed at two previous operations. Uterus left in situ with a Crossen suspension. Menstrual history 15 × 3 × 30. For two years previous to operation she menstruated every two weeks for ten or eleven days, with a profuse painful flow. Last period four months previous. Flushes with headaches began soon after operation. Bimanual examination revealed a small uterus which was in anterior position, not freely movable. Adnexa not palpable. Uterine measurement was 2½ inches.

Two successive complete twenty-four-hour urine specimens (1,770 and 1,730 c.c.) were assayed for estrin and none found. For seven days one tablet of progynon DH (600 units) was taken daily. Complete twenty-four-hour specimens were submitted on the second, fourth, and seventh days and two specimens were submitted one and three days, respectively, after the ingestion of the last tablet. (Results are noted in Fig. 1.)

After a protracted interval scanty tisue was obtained by biopsy. Microscopic examination revealed atrophic remnants of an early follicular phase. For a period of twelve days, the patient ingested eight tablets daily, a total of 4,800 units of the

progynon DH tablets (600 units). Flushes disappeared after the third day of medication. For a succeeding period of twelve days, the patient ingested 7,200 units daily in addition to daily injections of 5 International Units of proluton, a total of 60 International Units. Slight staining began a day before cessation of medication. Biopsy revealed endometrium of a luteal phase (Fig. 6). The patient described manifestations of impending menstruation during the last three days of medication in addition to breast fullness and nipple sensitivity during the last ten days of medication. There were no hot flushes after the third day of medication. The vaginal mucosa was pinkish and moist, the cervix assumed its normal softness; the uterus measured 2½ inches. Three days following termination of therapy there was definite bleeding for four days.

CASE 4.—J. G., white, female, aged 24 years, single, complained of severe hot flushes occurring every ten to fifteen minutes, lasting two to three minutes with attacks of profuse perspiration, followed by cold, clammy sweats.

Following two induced abortions, the second of which terminated in pelvic inflammatory disease, an appendectomy and removal of the right tube and ovary were done, and a second operation was necessary for removal of the left tube and ovary seven months later. Bimanual examination revealed a small retroverted uterus, deviated to the left, measuring 2½ inches. The introitus admitted two fingers with difficulty, the vaginal mucosa was pale and dry, cervix slightly atrophic.

Menstruation began at 13 × 3 × 28. There had been no menstruation for two months. Endometrial biopsy produced a scant amount of tissue which on microscopic examination revealed atrophic endometrium of an early follicular phase.

For a period of twelve days the patient ingested 4,800 units of progynon DH tablets daily. For a succeeding interval of twelve days, 7,200 units were ingested daily in addition to the injection of 5 International Units of proluton, a total of 55 International Units. Biopsy following the medication revealed endometrium of a follicular phase. The uterus measured 3¼ inches. The vaginal mucosa was moist, of a normal pinkish hue, the cervix was soft and of normal color, and there was slight sanguineous oozing from the external os.

The flushes and attacks of perspiration gradually disappeared until the day of the second biopsy when the patient experienced only one flush per day. A sanguineous discharge appeared during medication and three days of bleeding began on the twenty-first day of medication. Four days after cessation of organotherapy the patient experienced six flushes per day. Twelve days after cessation of organotherapy the patient reported the occurrence of only a few flushes a day.

CASE 5.—P. Z., aged 40 years, widow, was admitted to the Gynecological-Endocrine Clinic complaining of hot flushes every one-half to two hours, followed by attacks of excessive perspiration, joint pain over entire body, headache, and dizzy spells. Last menstrual period occurred eight months previously when a bilateral salpingo-oophorectomy for cystic ovaries was performed. Bimanual examination revealed a small atrophic retrodisplaced uterus measuring 2½ inches. Vaginal mucosa dry and pale. Cervix very atrophic and dilatable under extreme difficulty. Endometrial biopsy revealed atrophic remnants of an early follicular phase.

Eight tablets daily of ethynyl estradiol (1.2 mg.) were taken for twelve days. No recurrence of symptoms during the entire time of medication. Hot flushes and dizziness disappeared. Endometrial biopsy on the thirteenth day showed a good late follicular phase. The vaginal mucosa was moist and of a normal pinkish hue. Cervix easily dilatable. After a two weeks' interval, 12 progynon DH tablets (600 ABU) were taken daily for twelve days followed by eight progynon DH tablets daily for twelve days plus one ampoule of proluton (5 International Units) daily. Slight staining occurred during medication. Endometrial biopsy showed an early luteal phase with cystic degeneration. Nuclei of the glandular epithelium were centrally placed with a clear basal zone present. In some areas there was beginning tufting. Four days of bleeding occurred six days after cessation of medication. At this time the patient was completely free of symptoms. One month later the flushes recurred. At this time the same medication was repeated for twenty-four days.

The biopsy revealed several areas of endometrium which definitely showed changes ranging from early luteal to late luteal phase. At this time the patient was again completely symptom-free.

CASE 6.—C. L., white, married, aged 28 years, was admitted to Gynecological-Endocrine Clinic complaining of hot flushes and nervousness, excessive perspiration, especially during the night, and frequent frontal headaches. Bilateral salpingo-oophorectomy four years previously for bilateral dermoid cysts. Menstrual history 13 × 4 with irregular intervals. Two normal pregnancies and one spontaneous miscarriage. No menstruation since operation.

Bimanual examination revealed the uterus to be slightly smaller than normal, anterior position, freely movable, cervix small, well epithelized, uterus measured 2¼ inches. Endometrial biopsy revealed atrophic endometrium.

For a period of twelve days, the patient received eight progynon DH tablets daily (600 ABU). For a succeeding twelve days, 12 tablets daily were ingested in addition to the injection of 90 mg. of proluton in divided doses. Endometrial biopsy taken one day following the last injection revealed endometrium of a late luteal phase, uterus measured 3½ inches. At this time the hot flushes, attacks of perspiration, and headaches completely disappeared.

COMMENT

The majority of investigators agree that the normal corpus luteum secretes larger amounts of estrin than that of its predecessor, the mature Graafian follicle. This is obvious from the results obtained in blood examinations[4-6] of normal, fertile, menstruating women at various periods of the menstrual cycle, as well as consecutive urine examinations for estrin content. These findings are at variance with the opinion of Fluhmann,[7] who, on the basis of the test devised by him, reports the highest peak of estrin secretion just previous to ovulation and that a secondary rise appears prior to the onset of menstruation. Of primary importance, however, is the established fact that estrin is secreted during the entire normal cycle with the exception of the desquamative period, and the aggregate amount during the luteal phase is greater than that of the follicular phase. Another accepted fact is that a fully "estrinized endometrium" is necessary for progesterone to produce the luteal phase.

Hisaw and Leonard[8] originally stated that progestin could not transform rabbit endometrium, after castration atrophy, into a progestational condition. After further experimentation, Hisaw[9] alone reports mild, though definite, progestin changes in a juvenile monkey thirty-eight days after castration, giving 4 rabbit units of progestin daily for ten days. In the same paper he also reports a pre-secretory luteal effect, one far more pronounced than in the previous experiment, in an adult castrated monkey following the daily injection of 40 rat units of estrin for twenty-two days, followed by the combination of 73 rat units of estrin plus 4 rabbit units of progestin daily, for a period of ten days. In a third paper, Hisaw and his co-workers[10] report the production of progestational endometrial modification in castrated monkeys and rabbits with large doses of progesterone, small doses having little or no effect.

Animal experimentation, although of importance, does not necessarily always apply to changes in the human economy and consequently experimental efforts should be directed toward human criteria whenever possible. Very little experimental work with the human castrate uterus has been reported, with the exception of that of Kauf-

mann,[11, 12] Clauberg,[13] Elden,[14] Werner and others,[15-17] and myself.[1] Working independently of each other, the first two investigators succeeded in producing a luteal phase of endometrium in the human castrate by the daily injections of 10,000 mouse units of progynon benzoate for twenty-one days followed by 5 rabbit units of progestin (proluton) daily for seven days. Peculiarly enough, Elden and myself have been unable to corroborate these results, using 10,000 rat units of progynon B for five doses, followed by a total of 50 rabbit units of proluton, given in divided doses. Bleeding occurred within forty-eight hours after the last injection, as it did in the cases reported by Kaufmann and Clauberg. Case 1 (Fig. 3) is illustrative of this finding; the endometrial biopsy demonstrating a late follicular phase but no evidence of any luteal changes. Elden feels that several factors are involved, i.e., excess estrin, deficient progestin, or lack of balance between the two hormones. In three patients with long standing amenorrhea John Rock[18] reports that a total of 40 rabbit units of proluton caused demonstrable progestational changes in endometrium previously made to proliferate with huge doses of progynon B (50,000 rat units). These patients, however, possessed intact ovaries. The fact that estrone is secreted throughout the cycle should be emphasized, because my personal experiments in 6 human castrates were based on this knowledge. In a paper published in 1935 Kaufmann[19] alters his original therapeutic plan by increasing the dosage of estrin, i.e., 250,000 International Units of estrin for five doses every fourth day followed by five daily doses of 7 rabbit units of proluton. The total dosage of 1,250,000 International Units is equivalent to approximately 250,000 rat units, five times the original amount used. A late luteal phase was produced and the subject of Kaufmann's experiment began to bleed forty-eight hours later.

The present communication contains a departure from previous experimental procedures, not only as to the timing of medication but also utilizing the oral ingestion of estrin. Complete twenty-four-hour urinary specimens prior to treatment revealed the complete absence of estrogenic substances with the exception of Case C. M. (Fig. 1). Daily bio-assays following ingestion showed the presence of fairly large amounts of estrogenic substance, proving conclusively the biologic potency of the hormone used. In addition, urinary specimens received several days after final ingestion continued to show evidence of the hormone, indicating its cumulative action (Fig. 1).

In Case 1, 84,000 Active Biologic Units of dihydroxyestrin orally produced an active follicular endometrium, while in Case 2, 36,000 units for a period of fifteen days produced a mid to late follicular phase of endometrium. Again, in Case 2, after the administration of 72,000 Active Biologic Units of dihydroxyestrin followed by 20 International Units of proluton in divided doses, the biopsy specimens did not show the presence of glycogen nor a luteal phase of endometrium. The failure in this instance was undoubtedly due to the small dosage of progestin. Two months later the ingestion of 144,000 Active Bio-

logic Units of progynon DH for twenty-four days in addition to 60 International Units of proluton for the last twelve days produced a luteal phase. The third and fifth cases received similar amounts of the respective hormones within the same time limit, with the exception that the amount of estrin was reversed, i.e., 4,800 units daily for twelve days, followed by 7,200 units daily for twelve days, and here again luteal phases were produced in both instances. In these 2 cases the endometrial changes were more pronounced than in Case 2. In Case 4 there was bleeding for three successive days during the course of progestin therapy. For a period of two days the patient failed to receive proluton injections because of her illness. This, however, does not seem to corroborate the estrin deprivating theory, for she continued the estrin therapy without interruption for twenty-four days. A resumption of the progestin therapy failed to produce any luteal changes, therefore it may be assumed that complete desquamation occurred during the period of bleeding. Since an early follicular phase was found in the endometrial biopsy, the progestin was doubtless ineffective during the latter half of treatment. In Case 6 the additional amount of progestin injected produced a later luteal phase comparable to that found just before menstruation in normal individuals. In all but one instance (Case 4), the vasomotor disturbances were completely relieved soon after beginning organotherapy, and yet shortly after discontinuing medication a recurrence of symptoms occurred in two cases. The disappearance of the menopausal syndrome is due to the estrin-progestin inhibition of the pituitary, despite the fact that it is only temporary. In all six cases bleeding began within forty-eight to ninety-six hours after medication was discontinued, although occasional staining (sanguineous discharge) appeared during medication. Some patients described symptoms of impending menstruation toward the end of treatment. In all instances there was definite evidence of uterine development, as determined by differences in length when the uterine cavity was measured before and after treatment. The atrophic condition of the vaginal mucosa and cervix regained a normal pinkish hue and moisture. Breast fullness and nipple sensitivity were described in all cases.

It is only possible to theorize regarding the practical application of this experimental work at the present time. The same therapeutic methods are now being utilized in the treatment of primary and secondary amenorrheas, particularly in cases in which the pituitary-ovarian relationship is within normal limits.

SUMMARY

Of 6 castrated human females a luteal phase of endometrium was produced in three by the administration of 144,000 ABU of progynon DH orally and 55 to 60 rabbit units of proluton, and in a fourth with an additional 30 units of proluton. In one case, following the method of Kaufmann, a luteal endometrium could not be obtained. In another instance bleeding began with the administration of progestin which

nullified a possible progestin effect.   In all cases bleeding occurred during administration or after cessation of medication.   The hot flushes and other symptoms characteristic of the menopausal syndrome were completely relieved during the period of treatment, but recurred in all cases some time after cessation of medication.

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THE ANTERIOR PITUITARY-LIKE HORMONE IN LATE PREGNANCY TOXEMIA*

A SUMMARY OF RESULTS SINCE 1932

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THE presence of abnormally high levels of the anterior pituitary-like hormone† in the serum and urine of patients with late pregnancy toxemia and eclampsia was first reported in 1933.[2] This finding has since been confirmed.[3-6] Quantitative assays of the anterior pituitary-like hormone in the serum and urine of patients during normal and pathologic pregnancies are still being carried on in this laboratory and at the present writing (March, 1939) 560 serums and 390 urines from 173 pregnant women have been titered. Results concerning 127 of these pregnancies have been previously reported in

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detail.[2, 7-10] The total data which have accumulated during the seven years since the inception of this investigation seem sufficient to warrant separate summary.

Although urines and placentas from a large number of the cases included in this report have been assayed for the anterior pituitary-like hormone, the results of serum analyses only will be summarized. In the main, the findings in urines and placentas have been confirmatory of the serum titers, but the method for extracting the anterior pituitary-like hormone from the serum (see below) is more reliable than are those for urine or placental tissue. Moreover, the quantitative determination of any urinary constituent depends upon the accurate collection of a twenty-four-hour specimen. This can be accomplished only under the most rigidly supervised conditions, whereas the collection of blood involves no such chance for error. We have, therefore, in recent years come to rely almost entirely upon serum values. Furthermore, in any attempt to predict late pregnancy toxemia one must necessarily assay serum, since the urinary values for the anterior pituitary-like hormone do not rise to abnormal levels until toxemia has become clinically manifest, whereas excessive amounts in the serum are demonstrable four to six weeks prior to the development of toxic signs.[10]

Our criteria for normal levels of the gonadotropic factor in pregnancy are based upon the analyses of 210 serums from 64 patients who were normally pregnant and continued so to delivery. In 36 of these cases, serum assays were performed at intervals from as early as the sixth week of gestation to delivery. The rest were studied by single specimens during the last trimester. A peak in the curve of the anterior pituitary-like hormone in both the serum and urine has been found to occur at about the time of the second missed period,[10-13] the values at this time being frequently as high as or higher than those observed in cases of chorionepithelioma or hydatidiform mole. This high level, however, is maintained for only a comparatively short time, one to three weeks, a fact which supplies an important means of differentiating between early pregnancy and mole. By the beginning of the fourth month the anterior pituitary-like hormone of serum and urine has reached a constant low level and in no instance of normal pregnancy between the fifth and eighth months have the serum values been higher than 100 R.U. per 100 c.c. During the last four weeks of gestation in a number of cases the serum anterior pituitary-like hormone rose somewhat above this amount. Values above 100 R.U. per 100 c.c. prior to the fifth missed period or within four weeks of term are therefore not considered abnormal.

In Table I the 173 cases studied in late pregnancy have been divided into those with normal and those with high levels of anterior pituitary-like hormone. None of the 11 with a clinical diagnosis of nephritic toxemia or essential hypertension had elevated serum anterior pituitary-like hormone—that these cases were probably diagnosed correctly is supported by the fact that signs were present by the second trimester. A total of 13 women had premature deliveries, 5 of these with normal and 8 with excessive amounts of anterior pituitary-like hormone. Of the 85 patients

TABLE I. SERUM ANTERIOR PITUITARY-LIKE HORMONE IN LATE PREGNANCY.
SUMMARY OF TOTAL RESULTS. 1932 TO FEBRUARY, 1939, INCLUSIVE. 173 CASES

CLINICAL DIAGNOSIS AT TIME OF DELIVERY	PATIENTS WITH NORMAL ANTERIOR PITUITARY-LIKE HORMONE	PATIENTS WITH HIGH ANTERIOR PITUITARY-LIKE HORMONE
Normal pregnancy	64, 71.1 per cent	
Pre-eclampsia or eclampsia	10,* 11.1 per cent	75, 90.3 per cent
Nephritic toxemia	9,† 10 per cent	
Essential hypertension	2,† 2.2 per cent	
Premature delivery at 6 to 8 months	5, 5.6 per cent	8, 9.7 per cent
Totals	90	83

*Two of these patients died of eclampsia (1 came to autopsy). Two others are
known to have gone through a subsequent pregnancy with no toxemia.
†Symptoms began early in pregnancy.

classed as pre-eclamptic or eclamptic, 75 had high values for serum anterior pituitary-
like hormone and 10 had normal levels. Thus there were no normal pregnancies
among the 83 patients with high anterior pituitary-like hormone, 90 per cent having
been diagnosed as having pre-eclampsia or eclampsia and the other 10 per cent
having delivered prematurely.

Table II summarizes 82 of the above 173 patients who were followed from the
fifth month by repeated serum analyses with the purpose of determining whether

TABLE II. SUMMARY OF RESULTS OF REPEATED ANALYSES FOR SERUM ANTERIOR
PITUITARY-LIKE HORMONE DURING THE FIFTH, SIXTH, AND SEVENTH MONTHS OF
PREGNANCY. 82 CASES

CLINICAL DIAGNOSIS AT TIME OF DELIVERY	PATIENTS WITH NORMAL ANTERIOR PITUITARY-LIKE HORMONE	PATIENTS WITH ABNORMAL RISE
Normal pregnancy	36, 72 per cent	
Pre-eclampsia	2, 4 per cent	25, 78 per cent
Nephritic toxemia	6,* 12 per cent	
Essential hypertension	1,* 2 per cent	
Premature delivery at 7 to 8 months	5, 10 per cent	7, 22 per cent
Totals	50	32

*Symptoms began early in pregnancy.

or not late pregnancy toxemia could be predicted prior to its clinical manifestation
on the basis of serum anterior pituitary-like hormone values. In none of the 7
patients diagnosed as having nephritic toxemia or essential hypertension were the
values at any time above the limits of normal. Twelve women had premature de-
liveries, 5 with normal and 7 with high levels of serum anterior pituitary-like
hormone. *Of the 27 women who developed pre-eclampsia after the seventh month,
25 had had an unmistakable rise in serum anterior pituitary-like hormone four to
six weeks previously.* Two women, in whom repeated serum analyses failed to reveal
any abnormality, later developed toxemia. Thus none of the 32 women whose
serum values exceeded normal levels during the fifth, sixth, or seventh month ex-
perienced a continued uneventful gestation. Twenty-five developed pre-eclampsia*
and 7 delivered prematurely at about the time when toxic signs might have been
expected to appear.

CONCLUSIONS

1. Pre-eclamptic toxemia and eclampsia are usually (88 per cent in
this series) characterized by the finding of excessive amounts of an-

*It should be emphasized that, although the highest values for serum anterior
pituitary-like hormone have been encountered in cases of eclampsia, the degree of
excess of this factor does not consistently bear a direct relationship to the severity
of symptoms and signs.

terior pituitary-like hormone in the serum. This excess has been found to precede clinical signs by four to six weeks.

2. In a small percentage of cases with a clinical diagnosis of pre-eclampsia or eclampsia, the serum anterior pituitary-like hormone does not exceed normal levels.

3. In patients quite definitely diagnosed as nephritic or hypertensive (symptoms beginning earlier in pregnancy), the serum anterior pituitary-like hormone is normal.

4. Premature delivery may or may not be associated with excessive anterior pituitary-like hormone.

5. The finding of high levels of this substance in the serum during the fifth, sixth, or seventh month warrants the prediction of impending pre-eclampsia or premature delivery.

Quantification of serum anterior pituitary-like hormone during the fifth, sixth, and seventh months of pregnancy has become an accepted procedure both in this laboratory and at the New England Deaconess Hospital (Boston), where diabetic patients (in whom the incidence of premature delivery and pre-eclamptic toxemia is high) are being studied.* It has been found of considerable value as a means of predicting later trouble and governing the management of patients. For this reason it seems advisable to include in this report an exact description of how these tests are performed.

At two- to three-week intervals between the fifth and eighth months of pregnancy, 10 c.c. of venous blood are collected without any anticoagulant and the clot allowed to form. The serum is separated, cleared of any cells by centrifugation and measured accurately into four 15 c.c. centrifuge tubes, each tube to contain 1.0 c.c., 0.5 c.c., 0.5 c.c., and 0.3 c.c., respectively. About 10 c.c. of 95 per cent ethyl alcohol† are added to each tube, the contents mixed and the tubes placed in the refrigerator for twelve to 18 hours. After centrifuging and pouring off the supernatant alcohol, the precipitate is washed (stirring rod and shaking) once with ether, approximately 12 c.c., and again centrifuged. The ether is then poured off and the tubes allowed to drain for a few minutes, after which 3 c.c. of normal saline is added and mixed

with the precipitate, forming a smooth emulsion. The ether held back by the precipitate and saline is removed by stirring the contents up onto the sides of the centrifuge tubes while rotating, warming with the hand and blowing into the tubes. (No more heat than this should be applied—to avoid the possibility of any destruction of the hormone.) The stirring rods are washed down with 3 c.c. of saline, making the total content of each tube 6 c.c., this being the final test solution.

Each extract is administered subcutaneously into a nineteen- to twenty-one-day-old female rat, the injections being given twice a day for three days, 1 c.c. per injection. On the morning of the fifth day (ninety-six hours from the first injection) the rats are sacrificed and the ovaries examined for the appearance of *grossly visible discrete corpora lutea*. The anterior pituitary-like hormone of the serum being tested is considered normal provided none of the test animals or only the animal receiving the extract of 1.0 c.c. (test for 100 R.U. per 100 c.c.) gives a positive result. If all the animals show discrete corpora, the serum may be said to contain more than 333 R.U. of anterior pituitary-like hormone per 100 c.c., a definitely elevated level. If the animal receiving the extract of 1.0 c.c. and the 2 animals receiving the extract of 0.5 c.c. are positive, whereas the fourth animal has no corpora lutea, the serum may be said to contain 200 R.U. of anterior pituitary-like hormone per 100 c.c., an amount exceeding normal. For clinical purposes only 4 such tests are required with any 1 serum, unless the test for 333 R.U. per 100 c.c. is negative and the 2 tests for 200 R.U. per 100 c.c. fail to give check results. In this event the test for 200 R.U. per 100 c.c. is repeated on 2 more immature rats, and if more than 1 of the 4 animals receiving an extract of 0.5 c.c. show definite corpora, the anterior pituitary-like hormone may be considered to exceed normal levels.

Inasmuch as the reading of the end point requires considerable experience and even then is not always clear-cut, the importance of making check determinations with further specimens from the same patient and of using a series of at least 4 tests for each serum cannot be over-emphasized. No patient should be reported as having excessive anterior pituitary-like hormone unless high values are acquired in at least 2 specimens of serum.

DISCUSSION

It is logical to assume that the abnormal rise of serum anterior pituitary-like hormone, being the earliest indicator both of an hormonal imbalance and of impending pre-eclampsia or premature delivery, is most closely associated with the *primary* etiology. This, however, is not the only hormonal abnormality which has been found to characterize the disease. Quantitative determination of the estrogens has revealed that these are relatively low in the urine, serum, and placentas of toxemic patients.[2, 7-10] Urinary pregnandiol (the excretion product of progestin) has also been found to be below normal levels.[14, 15, 19] A detailed study of urinary estrogens,[14, 19] in which 3 different estrogenic factors have been assayed separately, indicates that progestin deficiency results in a marked change in the metabolism of the estrogens and in their more rapid destruction. Evidence for such a progestin-deficient metabolism of the estrogens has been found thus far in 8 pre-eclamptic patients at the time of the development of toxic signs.[17] The hypothesis has been proposed that some change associated with a faulty metabolism of the estrogens due to progestin deficiency (such as a toxic estrogen breakdown product) may be directly responsible for the generalized vascular derangement of pre-eclampsia and eclampsia.[14] Whether or not this hypothesis proves to be correct, our quantitative

studies of pre-eclampsia point toward the following sequence of events: (1) Excessive amounts of circulating anterior pituitary-like hormone, (2) a decrease of progestin and "total" estrogen at a time when they normally increase, and (3) a striking change in the metabolism of estrogens due to reduced progestin, this last abnormality being demonstrable at the time of the onset of clinically recognizable toxemia. The role of anterior pituitary-like hormone, which distinguishes human pregnancy from that of practically all other mammals, in the physiology of normal gestation has not been ascertained, but one naturally supposes that this gonadotropic factor plays an important part in the placenta's elaboration of progestin and estrogen, since it is such a potent stimulator of these factors from the ovaries of experimental animals.   Of course the placenta has not been proved the source of progestin and estrogen, but the circumstantial evidence pointing toward it as the source is overwhelming.   There come to mind 3 possible explanations for the apparent paradox introduced by the finding of high levels of anterior pituitary-like hormone together with a deficiency of progestin and estrogen in pre-eclampsia.   (1) The increase of the gonadotropic substance may be a protective measure, an attempt to counteract a failing production of progestin and estrogen.   If this explanation were correct, one would expect the increase to follow rather than precede the drop in urinary estrogens and pregnandiol.   (2) Excessive amounts of anterior pituitary-like hormone, due to an imbalance of placental function, over a sufficiently long period may have, in certain patients, an inhibitory influence upon the secretion of progestin and estrogen, just as its prolonged administration experimentally is known to result in ovarian atrophy due to the stimulation of antibodies.   If this were the case, the presence of antibodies in the material being assayed would inhibit the reaction and depress the titer.   (3) To us, the most plausible explanation lies in a failing utilization of anterior pituitary-like hormone in the production of these steroids and consequent building up of the level of anterior pituitary-like hormone in the blood.   This third hypothesis is supported by the following considerations.   In normal pregnancy a rapid decline in the level of anterior pituitary-like hormone takes place during the third and fourth months.   This decline coincides both with a rapidly increasing elaboration of estrogens and progestin (based on urinary estrogen and pregnandiol) and with the "taking over," presumably by the placenta, of the functions of the regressing corpus luteum.   These events are in accord with the idea that anterior pituitary-like hormone is utilized normally for the secretion of estrogen and progestin by the placenta, and that, in being so utilized, its level in the circulation is kept low.   Since the low level of serum anterior pituitary-like hormone is maintained during the fifth, sixth, and seventh months of normal gestation, during which time the production of estrogens and progestin steadily increases, an abnormal rise would be interpreted as failure of utilization.   On this basis one would place the primary etiology of pre-eclampsia in whatever causes the

placenta to be deficient in the utilization of anterior pituitary-like hormone for production of estrogen and progestin. It is entirely conceivable that a failing utilization of anterior pituitary-like hormone might be accompanied by decreased formation in which event no abnormality would be revealed by its quantification. It is further conceivable that decreased formation might result from damage to the placenta by toxic separation, pre-eclampsia, or eclampsia. Such situations could explain the normal values for serum anterior pituitary-like hormone found in 12 per cent of the pre-eclamptic and eclamptic patients as reported above.

The fact that 22 per cent of the patients in whom an abnormal rise of serum anterior pituitary-like hormone was detected during the fifth, sixth, and seventh months delivered prematurely deserves comment. All the factors involved in the initiation of labor have not been ascertained but quantitative studies in women have revealed a marked drop in estrogens just before delivery,[16, 17, 19] and a decrease in progestin has also been indicated by the changed metabolism of the estrogens which accompanies normal labor.[17, 19] The same hormonal changes which precede and accompany the onset of pre-eclampsia, therefore, appear to pertain rather suddenly at the time of normal delivery. Under certain conditions these changes might be associated with premature delivery rather than toxemia.

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The author believes that the practical value of repeated vaginal smears is not recognized sufficiently because of technical difficulties in staining them. He suggests fixing in equal parts of alcohol and ether, in which the slides can be kept indefinitely. Before staining, the slide is covered with methyl alcohol for two minutes, and then stained with diluted Giemsa prepared by adding 10 drops of the standard solution of 5 c.c. of distilled water. Staining requires twenty minutes. Cornified cells are stained red, partially cornified ones violet, and noncornified cells blue.

CARL P. HUBER.

THE EFFECT OF CRYSTALLINE CORPUS LUTEUM HORMONE, PROGESTERONE, ON THE OVARIES AND RELATED ENDOCRINE ORGANS

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THE recent availability of chemically pure corpus luteum hormone and its increasing employment as a therapeutic agent emphasize the importance of re-examining the accumulated experimental data (derived from the use of the crude product) on the effect of the hormone on the ovaries and related endocrine glands. Following Beard's[1] suggestion that the presence of the corpus luteum prevents ovulation during pregnancy, many corpus luteum extirpation experiments supported the thesis that the corpus luteum hormone suppresses follicular activity and inhibits ovulation.[2-4] It was shown later that the administration of impure progestin-containing extracts temporarily suppresses both growth of ovarian follicles (with loss of estrous cycles) and ovulation in rats,[5, 6] guinea pigs[7-11] and in rabbits.[12-14] While such laboratory data should not be too eagerly translated into clinical equations, their importance to gynecology cannot be lightly estimated. If, as indicated in the earlier experiments, the corpus luteum hormone really inhibits follicular growth and ovulation, it must be administered with circumspection to women of childbearing age, although in some instances hormonal sterilization as attempted by Haberlandt[15] may be desirable.

It is certainly conceivable that some of the biologic effects previously attributed to progestin may have been caused by the presence of contaminants, such as injurious chemicals or small quantities of estrogen, in the progestin-containing extracts. The degeneration of the liver as well as of the ovaries, observed by Kennedy[12] in rabbits treated with an impure extract of corpora lutea, is mute testimony to the presence of unknown toxic agents in the product he employed. The admixture of estrogen in the early preparations of progestin was responsible for certain effects formerly believed to be specific for the corpus luteum hormone. For instance, both relaxation of the pubic joint[16] and vaginal mucification[17] have been recently elicited by administration of subminimal doses of estrogen alone.[14, 18] These changing concepts concerning the true physiology of the corpus luteum hormone make re-investigation with progesterone imperative. This has already been accomplished in reference to the uterine effects of progesterone. The pure product does inhibit uterine motility and converts the estrogen-primed endometrium into a pregravid state.[19]

Investigation of the effects of progesterone on the ovaries was, to the best of our knowledge, thus far attempted by three groups of investigators, with discordant results.

Shapiro and Zwarenstein[20] have found that progesterone causes ovulation in the normal and hypophysectomized amphibian. McKeown and Zuckerman[21] have likewise found fresh corpora lutea and mature follicles in normal cyclic female rats which had received 1 mg. of progesterone daily for from nine to eleven days despite the suppression of the estrous cycles in 6 of the 7 animals. Selye, Browne and Collip,[22] on the other hand, have found that the daily administration of 4 mg. of progesterone for a period of twelve days in normal cyclic rats causes inhibition of follicular growth and atrophy of the ovaries.

The need for re-investigation of the effect of chemically pure progestin on the ovaries and related endocrine glands is evident from the foregoing summary of the problem. The experimental work herein reported was undertaken with this objective in view.

METHOD

Employing adult rats, three series of progesterone-injection experiments were executed as follows:

Experiment I.—Sixteen adult, female rats were each given subcutaneously 0.5 mg. of progesterone* in 0.2 c.c. of sesame oil 3 times weekly for nine and one-half weeks (sixty-seven days). The total amount of progesterone administered to each rat during the course of sixty-seven days was 14.0 mg. Ten additional, adult, female rats, serving as controls, were each given subcutaneously 0.2 c.c. of sesame oil for an equal length of time.

Experiment II.—Six adult, female rats were each given subcutaneously 1.0 mg. of progesterone in 0.1 c.c. of sesame oil *daily* for thirty days. An additional group of 6 adult, female rats, serving as controls, were each given 0.1 c.c. of sesame oil daily for the duration of the experiment.

Experiment III.—Five adult, female rats were each given subcutaneously 4.0 mg. of progesterone in 0.4 c.c. of sesame oil *daily* for twelve days. The total amount of progesterone administered to each rat, during the course of twelve days, was 48 mg. Each of five additional animals, serving as controls, received 0.4 c.c. of sesame oil daily.

Daily vaginal smears were made and the estrous cycles recorded. All animals in each series were killed on the day following the last injection of progesterone. The ovaries, pituitary gland, and adrenals were extirpated, weighed and examined microscopically (Table I, Figs. 1 to 4).

RESULTS

Effect on the Ovaries.—The weight and morphology of the ovaries were unchanged by the sixty-seven-day course of treatment with 0.5 mg. of progesterone thrice weekly. Growing follicles, in all stages of development, and multiple fresh corpora lutea were present in the ovaries of both the treated and control groups of animals (Figs. 1 and 2).

The average weight of the ovaries in the two groups of rats which received the larger quantities of progesterone over a shorter period of time was somewhat lower than that of the respective control groups. This was especially apparent in the 4 mg. series (Table I). The microscopic appearance of the ovaries betrayed the deleterious effects of what may be assumed to be excessive doses. There were fewer growing follicles and no fresh corpora lutea. However, even the largest quantity of progesterone (4 mg. daily for twelve days) failed to suppress ovarian function entirely (Figs. 3 and 4).

*Proluton, a synthetic progesterone, was employed through the courtesy of Drs. Gregory Stragnell and Erwin Schwenk of the Schering Corporation, Bloomfield, N. J. Assayed in our laboratory, 1 mg. of proluton was found to equal a Corner rabbit unit.

Effect on the Pituitary Gland.—Recognizing that the entire subject of pituitary cytology is presently undergoing rigorous re-investigation[23] and wishing to avoid any dubious interpretation of questionable histologic alterations attributable to progesterone treatment, we are eliminating a description of the microscopic appearance of the pituitaries. Reliance is placed solely on relative weight in which there was
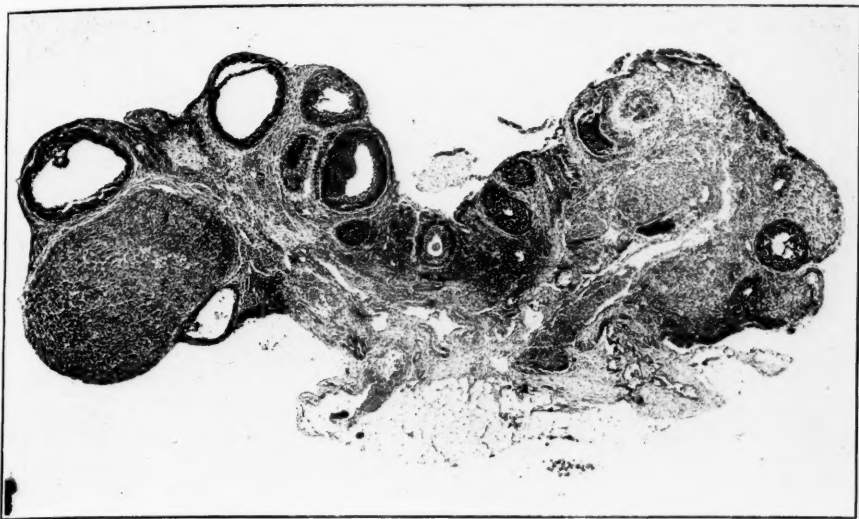
Fig. 1.—(Control.)   Photomicrograph of an ovary of an untreated adult rat, showing many mature follicles and a corpus luteum.   (×24.)
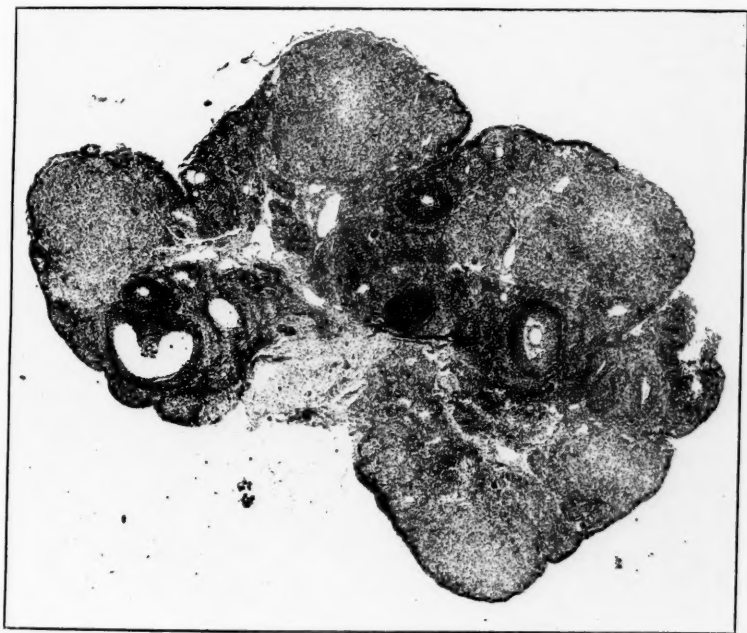
Fig. 2.—(Exper. I.)   Photomicrograph of an ovary of an adult rat injected with 0.5 mg. of progesterone every other day for sixty-seven days, showing mature follicles and well-developed corpora lutea.   (×24.)

no significant difference (Table 1). We are, nevertheless, not unmindful of the fact that functional inhibition may be present without change in weight of the organ. Considered, however, in the light of the undisturbed estrous cycles and the unchanged ovarian morphology in the 0.5 mg. series, the absence of pituitary weight changes suggests that physiologic quantities of progesterone cause no alteration in pituitary function of the rat.

Effect on the Adrenals.—The average weight of the adrenals of the three series of progesterone-treated rats did not differ from that of the control groups (Table
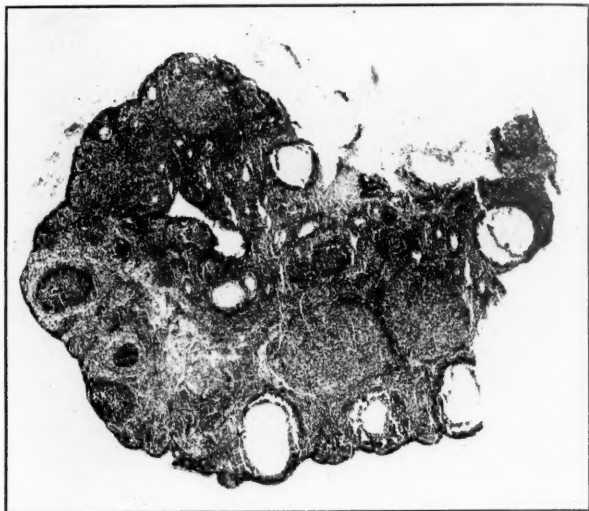
Fig. 3.—(Exper. II.) Photomicrograph of an ovary of an adult rat injected with 1.0 mg. of progesterone daily for thirty days, showing a decrease in size, degenerated follicles, and no fresh corpora lutea. ($\times$24.)
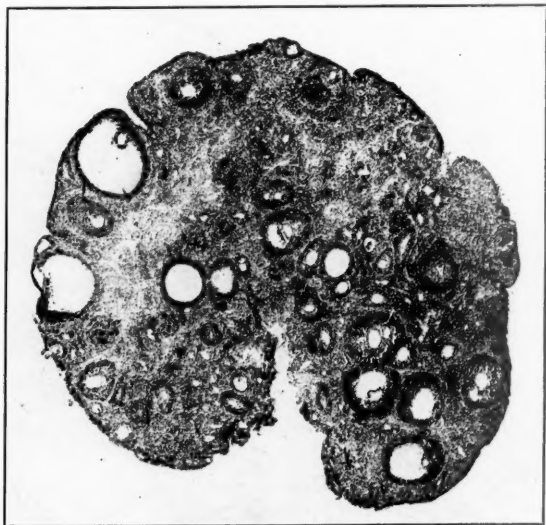
Fig. 4.—(Exper. III.) Photomicrograph of an ovary of an adult rat injected with 4.0 mg. of progesterone daily for twelve days, showing a decrease in size, many atretic follicles, and no corpora lutea. ($\times$24.)

TABLE I. EFFECT OF VARIED QUANTITIES OF PROGESTERONE ON THE AVERAGE WEIGHT
OF THE OVARIES AND RELATED ENDOCRINE ORGANS OF ADULT FEMALE RATS

	EXPERIMENT I		EXPERIMENT II		EXPERIMENT III	
	TREATED	CONTROL	TREATED	CONTROL	TREATED	CONTROL
No. of rats	16	10	6	6	5	5
Dose of progesterone	0.5 mg. e.o. day for 67 days	0	1.0 mg. daily for 30 days	0	4.0 mg. daily for 12 days	0
Body weight (gm.)	175	160	171	175	159	164
Ovaries (mg.)	51	54	42	56	38	50
Pituitary (mg.)	10	10	10.5	9.4	7.8	9.6
Adrenals (mg.)	39	35	42	42	37	39

I). Likewise, no striking histologic changes were noted in the adrenals of the treated animals, the architecture of the cortical zones and the vascularity of the medulla appearing the same in all groups.

Effect on Estrus.—Regular estrous cycles continued unabated at intervals of from four to five days in all rats which received 0.5 mg. of progesterone every other day for sixty-seven days. The average number of estrous cycles per rat during the course of sixty-seven days was 14 in the treated and 16 in the controls. All but 2 of the 6 rats which received 1.0 mg. of progesterone daily for thirty days continued to have regular estrous cycles at intervals of from four to seven days during the thirty-day period, despite the known tendency of progestin to inhibit *vaginal* estrus. Three of the 5 rats given 4 mg. of progesterone daily for twelve days had one estrous cycle near the termination of treatment and the remaining 2 were anestrus.

The uninterrupted periodicity of the estrous cycles in the first group, despite the chronic administration of progesterone, was naturally a reflection of undisturbed ovarian activity. The partial or complete loss of estrous cycles in the two groups of rats given the larger quantities of progesterone indicates that the hormone does, when given in quantities far above the physiologic level, depress follicular growth and maturation. It is, however, significant that even a quantity as large as 4 mg. daily for twelve days does not uniformly suppress the estrous cycles.

DISCUSSION

It is evident from the above-described experiments that the prolonged administration of progesterone in physiologic quantities does not inhibit follicular growth, ovulation, and luteinization in the normal cyclic rat as do other active sterones, such as estrogen[24] and testosterone.[25] This observation is corroborated clinically, since we and others have found that the administration of 10 mg. of progesterone daily to women during the second half of the menstrual cycle —a total quantity more than sufficient to produce a progestational endometrium in the estrogen-primed uterus of the castrated woman— does not interfere with the menstrual rhythm, either immediately or remotely. When, however, huge doses, far in excess of physiologic needs, are experimentally administered, follicular growth, ovulation and luteinization are inhibited.

The quantity of active hormone administered to each rat in the first experiment, namely, 0.5 mg. every other day for sixty-seven days, is far greater than that present in the *crude* extracts which produced follicular inhibition and is evidently more than sufficient for the species employed. In fact, the quantity received weekly (1.5 mg.) by each of the treated rats in Experiment I is more than sufficient to produce complete progestational changes in the endometrium of an estrogen-primed castrated rabbit weighing 3 kilograms. Moreover, the total dose (14 mg.) given each rat of this series is equal to the quantity of progesterone capable of suppressing the menstrual cycle of the adult monkey,[19] and is nearly half the quantity capable of evoking the secretory phase in the endometrium of an estrogen-primed human castrate.[26-28] Considered in the light of these data, it is fair to conclude that the absence of follicular inhibition in the first group of rats cannot be attributed to inadequate dosage.

The inhibition of follicular growth and the altered estrous cycles in the other two groups of rats attest to the harmful effect of unphysiologic quantities of progesterone. The larger the dose, the greater the follicular inhibition as seen in the group of rats given the largest quantity of progesterone, namely, 4 mg. daily for twelve days. This confirms the observations of Selye and his co-workers.[22] However, even a relatively large quantity such as 1.0 mg. daily for thirty days does not completely suppress follicular growth and uniformly inhibit estrus.

These experiments illustrate that it is the *total quantity* of progesterone and not the length of time of its administration which causes inhibition of follicular growth. Fourteen milligrams of progesterone administered over a period of sixty-seven days produced no deleterious effect, whereas double the quantity (30 mg.) spread over a period of only thirty days did produce considerable ovarian damage.

On the basis of these experiments and our clinical observations, we are justified in assuming that the clinical use of progesterone in doses of 5 to 20 mg. daily for a period of two weeks, and of smaller doses over a period of months, is safe.

SUMMARY

Unlike impure progestin products, progesterone, the crystalline corpus luteum hormone, administered in doses of 0.5 mg. thrice weekly for nine and one-half weeks to normal adult rats produced no inhibition of follicular growth, ovulation, and luteinization. The estrous cycles continued unabated. Nor was there any change in the average weight of the pituitary, adrenals, and ovaries. Evidence is adduced from the literature to emphasize that this quantity is more than enough for the physiologic needs of the rat.

Larger doses, such as 1 mg. daily for thirty days or 4 mg. daily for twelve days, produced definite inhibition of follicular growth and prevented ovulation and luteinization. These effects are apparently the result of excessive and obviously unphysiologic dosage.

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THE LIPID AMINO-NITROGEN IN ECLAMPSIA AND PRE-ECLAMPSIA

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THE blood lipids in patients with eclampsia and toxemias of pregnancy have been studied by several investigators.

Lindeman[1] showed that the blood lipids in eclampsia were high while the fats were low. Slemons and Stander,[2] as well as Helmuth,[3] found that there was no significant change in the lipids in whole blood in eclampsia. In an excellent study of the subject Boyd[4] concluded that there was no variation in any single lipid in either the red cells, white cells, serum, plasma, or whole blood, but that there was an elevation in the plasma cholesterol-phospholipid ratio. This change occurred consistently in cases of eclampsia but only very rarely in pre-eclampsia.

There has been no attempt to analyze the individual phospholipids. The present report is concerned with a study of the blood lipid amino-nitrogen in pre-eclamptic, eclamptic, and normal gravid women.

METHOD

The method of Kirk, Page and Van Slyke[5] for the determination of alpha amino-nitrogen in the alcohol-ether and petroleum ether extractives of whole blood was used. According to these authors the amino group is derived in large part from cephalin

and may be interpreted in general as an index of the level of blood cephalin. Normal values have been determined by Kirk, Page and Van Slyke[5] and by Andrus and Moore.[6] The latter investigators concluded that any value exceeding 2.00 mg. of alpha amino-nitrogen per 100 gm. of whole blood is definitely abnormal and indicative of liver damage.

A control group of 9 normal pregnant women was chosen and fasting blood samples were taken between the twenty-sixth and thirty-second week of pregnancy, between the thirty-third and thirty-seventh week of pregnancy, between the thirty-eighth week and term, and one week after delivery. The majority of this group were young primigravidas. In the pre-eclamptic and eclamptic groups, fasting blood samples were taken both ante partum and post partum. It was impossible to obtain samples from these women prior to the development of the toxemia. More than one sample was secured whenever possible and in the eclamptic group samples were taken frequently. While all of the pre-eclamptic cases studied were severe, the eclamptic cases have been classified as mild, moderate, and severe.

Table I shows the results obtained in the control patients; Table II those obtained in patients with pre-eclampsia; and Table III those in patients with eclampsia. In the normal gravidas, only two determinations out of 33, or 6 per cent, were above the upper normal limit of 2 mg. In the pre-eclamptic women, 23.5 per cent of the determinations exceeded the upper limit of normal, while in the eclamptic patients, 27.0 per cent exceeded this limit. Among the women with pre-eclampsia, 4 of the 8 showed an elevation above the normal on at least one occasion, while in the patients with eclampsia, 7 out of the 11 showed a similar elevation. It is worthy of note that the average increase paralleled the severity of the disease and that the 2 patients who died showed the highest values.

TABLE I.   CONTROL

	26-32	33-37	38-40	POST PARTUM
I.T.	1.44	1.13	0.54	1.20
L.V.	0.26	0.80		0.62
E.B.	0.94	0.28	1.23	2.13
A.L.	0.44	1.30	1.58	0.90
M.B.	1.22	0.49	0.82	1.40
M.K.	1.75	0.68	1.65	1.25
L.M.	0.41	1.77	0.48	1.55
D.C.	1.36			0.05
D.L.	1.36	0.30	0.76	2.26

All determinations are given in mg. of alpha amino-nitrogen of blood.

TABLE II.   PRE-ECLAMPSIA

	ANTE PARTUM		POST PARTUM	
L.B.	0.82	0.66	1.01	0.93
L.S.		1.40	1.64	
R.M.		0.55	0.74	
H.B.		2.30	3.30	
H.W.		2.78	1.45	
M.I.		1.02	0.22	
C.F.	1.07	0.91	2.11	
A.N.		1.34	0.90	2.28

All determinations are given in mg. of alpha amino-nitrogen of blood.

The results indicate a tendency toward an increase of the lipid amino-nitrogen of the blood in pre-eclampsia and eclampsia. Charles, Fisher, and Scott[7] have recently disputed the original tenet of Howell[8] that cephalin is the thromboplastic substance. Despite the evidence of these authors, which one of us (M) has partially confirmed,*

*Cephalin, prepared according to the method of Levine,[9] does not induce coagulation of peptonized plasma and may be injected intravenously into dogs in doses up to 800 mg. with impunity.

TABLE III. ECLAMPSIA

		ANTE PARTUM		POST PARTUM			
K.C.	Severe (died)	5.64					
T.R.	Moderate	1.31	2.41	0.40	1.43		
V.R.	Mild			3.61	2.54	1.62	0.79
F.	Moderate	1.73	1.12	0.87	1.92		
M.B.	Moderate			1.60	2.38	2.35	1.08
R.G.	Mild	1.40		1.08	1.82		
C.A.	Severe (died)	3.78	6.42				
E.G.	Mild	1.78		1.06			
J.F.	Moderate	2.70		1.59	0.74		
K.C.	Moderate	1.03	2.21	0.54	1.62		
G.F.	Mild	0.94		1.62			
A.B.	Mild			0.49	0.83	1.41	0.79

All determinations are given in mg. of alpha amino-nitrogen per 100 gm. of blood.

it must be granted that thromboplastin is a substance closely related to cephalin and is in the part of the lipid extractives of blood and tissues which contains amino-nitrogen. The increase of the lipid amino-nitrogen fraction of the blood is of interest in the light of Fahr's[10] conclusion concerning the fundamental lesion in eclampsia, a deposition of fibrin and thrombosis in the smaller branches of the portal veins and in the afferent arterioles of the glomeruli. If the lipid amino-nitrogen fraction of the blood contains the thromboplastic substance, and this is increased in eclampsia, it would be possible to account for the hepatic lesion on the basis of the increased coagulability of the blood. Dieckmann[11] attempted to increase the coagulation time in dogs by the injection of proteins and produced a lesion of the liver similar to, but not identical with that found in women with eclampsia.

On the other hand the increase of the lipid amino-nitrogen may be the result and not the cause of the damage to the liver, a conclusion more in accordance with the findings of Andrus and Moore,[6] who reported a similar increase in obstructive jaundice with severe liver damage. Further conclusions concerning the findings must await more exact knowledge of the nature of thromboplastin and the pathogenesis and etiology of eclampsia.

SUMMARY

There is a significant elevation of the blood lipid amino-nitrogen in the whole blood of eclamptic and pre-eclamptic women and the elevation parallels the severity of the toxemia.

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THE CLINICAL SIGNIFICANCE OF PELVIC VARIATIONS*

A Dimensional Study of the Upper, Mid, and Lower Pelvis in 200 White Primiparous Women

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THE development of precise roentgenometric methods during the past decade has revised our concepts of the architecture of the female pelvis, and has added a diagnostic technique of great practical value to clinical obstetrics. Several methods for roentgen pelvimetry have been described, but some of these are so complicated, and require the use of such elaborate equipment, as to make them unsuitable for use in the average roentgen laboratory. Moreover, in some instances the interpretation of results is an esoteric art which few roentgenologists or obstetricians have the time or inclination to master. These shortcomings have tended to create an impression that roentgen pelvimetry is more properly an exercise of research laboratories than the concern of the practicing obstetrician. The potential usefulness of a roentgenologic survey in the management of individual obstetric cases has not been generally realized.

The method which is briefly outlined in this communication is simple, rapid, and inexpensive, and, during the past four years, it has been used routinely in primigravid patients. The findings in 600 white women were recently published[1] but did not include the routine measurement of the midpelvic plane. In the present series of 200 cases this has been done and the chief purpose of this presentation is to record and analyze the data in this group of patients. As in the previous series, these were primigravid white women consecutively delivered at term (child 2,500 gm. or over) in the wards of the New Haven Hospital. It is our opinion that they present a fair sample of obstetric pelves in white women and so furnish criteria of normalcy without which abnormalities cannot be properly evaluated. This analysis of pelvic findings will be preceded by a discussion of the obstetrically important pelvic diameters, a brief outline of the technique of pelvimetry and a classification of pelvic variations.

THE IMPORTANT PLANES AND DIMENSIONS OF THE OBSTETRIC PELVIS

From the obstetric viewpoint there are three portions of the pelvis concerning which information is important. These are: (1) The plane of the pelvic inlet, (2) the midpelvic or narrow pelvic plane, and (3) the planes of the pelvic outlet. A

knowledge of the dimensions and contours of these planes of the pelvis will present useful knowledge of available pelvic space and will furnish an index of the architecture of the pelvis.

The Plane of the Pelvic Inlet.—This plane may be described as follows. It is bounded anteriorly by the upper posterior surface of the symphysis, laterally by the iliopectineal lines, and posteriorly by the upper anterior surface of the sacrum at the point where the iliopectineal lines would meet if they were to be continued posteriorly. In the individual pelvis this point may or may not be located at the promontory. It is usually somewhat below this process. It will be seen that the plane thus described is not that of the anatomic superior strait. Its importance as the obstetric inlet of the pelvis has been emphasized by Caldwell, Moloy, and D'Esopo[2] and others.

In addition to a knowledge of the shape of the plane of the pelvic inlet, there are three diameters which furnish useful information: (1) The anteroposterior diameter, (2) the transverse diameter, and (3) the posterior sagittal diameter.

The anteroposterior diameter extends from a point on the upper posterior surface of the symphysis about 1 cm. below the superior border to the anterior surface of the sacrum at the point where the iliopectineal lines would meet if they were to be continued.

The transverse diameter is the greatest distance separating the iliopectineal lines. It bisects the anteroposterior diameter somewhat posterior to its midpoint.

The posterior sagittal diameter is that portion of the anteroposterior diameter which is posterior to the point of intersection by the transverse diameter. It is useful as an index of the amount of space in the upper posterior pelvis. When abnormally shortened, it represents an abnormal posterior displacement of the transverse diameter.

The Midpelvic or Narrow Pelvic Plane.—This plane is also known as the plane of least dimensions and has been defined as extending from the lower border of the symphysis laterally through the ischial spines, then posteriorly to the tip of the sacrum. However, as Hanson[3] has pointed out, these points are not truly in the same plane, the tip of the sacrum often being 2 cm. or more below the proper level of the posterior part of such a plane. This author suggests that the posterior limit should be placed at the juncture of the fourth and fifth sacral vertebrae, and our studies of the lateral pelvic aspect have confirmed the soundness of his view.

The anteroposterior diameter of the midpelvic plane, therefore, extends from lower border of the symphysis through the bispinous diameter, and usually to the junction of the fourth and fifth sacral segments. (Rarely this posterior point is subject to variation, especially in sacra containing more or fewer than the usual number of segments.)

The transverse diameter of the narrow pelvic plane, also known as the bispinous diameter, is the shortest distance separating these projections.

The posterior sagittal diameter of the narrow pelvic plane is that portion of the anteroposterior diameter which lies posterior to its intersection by the bispinous diameter. This diameter gives a useful index to the available space in the posterior lower midpelvis and its length is modified by the size and shape of the greater sacrosciatic notch.

The Pelvic Outlet.—The pelvic outlet consists of two planes represented by two triangles, the bases of which join along the line of the bituberal diameter. The anterior triangle is bounded laterally and above by the bones comprising the pubic arch. The posterior triangle is bounded anteriorly by the bituberal diameter and its sides converge posteriorly to the tip of the sacrum. The important diameters of the outlet are the bituberal or transverse of the outlet, representing the widest separation of the lower inner surfaces of the tubera ischii and the posterior sagittal diameter which extends posteriorly from a midpoint on the bituberal diameter to the anterior surface of the tip of the sacrum. Other diameters, such as the anterior sagittal and anteroposterior, have been described as useful pelvic outlet measurements, but in our opinion they are without important obstetric significance.

SUMMARY

We consider the following diameters to be important in routine pelvimetry:

Pelvic Inlet

Anteroposterior
Transverse
Posterior sagittal

Narrow Pelvic Plane

Anteroposterior
Transverse (bispinous)
Posterior sagittal

Pelvic Outlet

Transverse (bituberal)
Posterior sagittal

The lengths of these diameters serve as an excellent index of the available space in the bony birth canal and also as a useful record in statistical studies of the pelvis. We wish also to emphasize the importance of certain contours which are visualized in the roentgenograms or ascertained by palpation. As will be noted below, the contours of the pelvic inlet and those of the lateral aspect of the pelvis are readily seen in the roentgenograms.

METHOD USED FOR ROUTINE PELVIMETRY

The pelvic inlet may be visualized and measured by the centimeter grid method of roentgen pelvimetry.[4] This consists of the projection of the pelvic inlet to the sensitive film with the patient in a semirecumbent position and the target at a 30 in. distance. Distortion due to the spread of the rays is corrected by the perforated centimeter grid which is placed in the plane of the pelvic inlet following the exposure and removal of the patient from the table. A second (flash) exposure reproduces small dots on the film, the distance between which represents centimeters in the plane of the inlet. All of the pelvic inlet diameters may be read directly. In addition, the outline of the inlet may be visualized as well as the side walls of the lower pelvis and the ischial spines. The distance between these processes (bispinous diameter) is also measured on this film, using a distortion table to correct spread of the rays for the level in which they rest. This level is determined in the lateral film.

The second roentgenogram depicts the lateral aspect of the pelvis and is taken with the patient standing laterally to the target which is placed at 5 foot distance. Distortion due to the spread of the rays is corrected by means of an opaque centimeter notched rod which is placed posterior to the patient and in the midplane of the body. A corrected scale is thus projected on the edge of the film and with calipers all of the anteroposterior diameters of the pelvis may be measured. On this film, therefore, we measure the anteroposterior diameter of the inlet, the anteroposterior diameter of the narrow pelvic plane, the posterior sagittal diameter of this plane, and the posterior sagittal diameter of the outlet. Also, in the lateral film we may visualize all of the important lateral contours of the pelvis, including the sacral curve and the character of the sacrosciatic notch.

For the determination of the intertuberal or transverse diameter of the outlet, we depend upon palpation and direct measurement. The contour of the lateral aspects of the pubic arch are also described after palpation. For routine purposes we have found these outlet palpatory methods quite as satisfactory as roentgenometry of this portion of the pelvis.
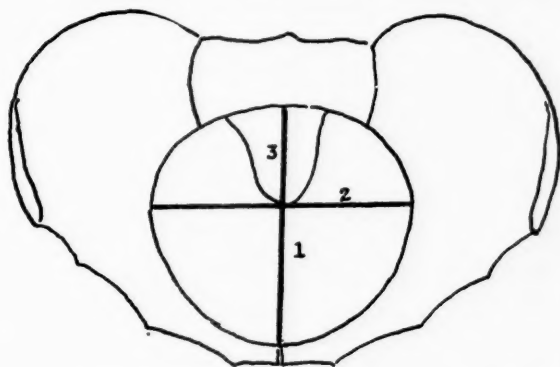
Fig. 1.—Diameters of the pelvic inlet. *1*, Anteroposterior diameter; *2*, transverse diameter; and *3*, posterior sagittal diameter.
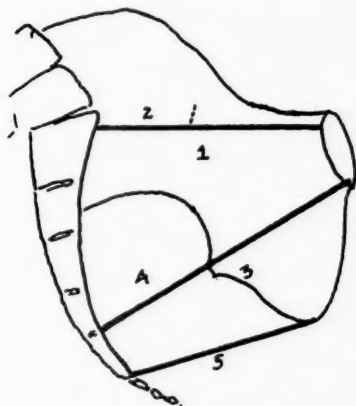
Fig. 2.—Diameters of the lateral pelvis. *1*, Anteroposterior diameter of inlet; *2*, posterior sagittal diameter of inlet; *3*, anteroposterior diameter of midplane; *4*, posterior sagittal diameter of midplane; and *5*, posterior sagittal diameter of outlet.

PELVIC VARIATIONS AND THEIR CLASSIFICATION

The chief contribution of roentgen studies in recent years is the recognition of definite variations in form of the female pelvis. Studies in this clinic and elsewhere have shown that for practical obstetric purposes female pelves may be divided into four general groups using the shape of the pelvic inlet as a basis for classification. The following variations in pelvic inlet conformation may be thus classified:

I. Dolichopellic or anthropoid type: The anteroposterior diameter exceeds the transverse diameter, the pelvis being elongated anteroposteriorly.
II. The mesatipellic or round type: The anteroposterior and transverse diameters are of equal length, or the transverse exceeds the anteroposterior by not more than 1 cm.
III. The brachypellic or oval type: The transverse diameter exceeds the anteroposterior by more than 1 cm. and less than 3 cm.
IV. The platypellic or flat type: The transverse diameter exceeds the anteroposterior diameter by 3 cm. or more.

In discussing pelvic variations we should not overlook certain changes characteristic of male pelves and spoken of as android changes, which

may affect various portions of the female pelvis. The android characters which may be found at the pelvic inlet are:

1. The curve of the iliopectineal lines is less arcuate and the transverse diameter is displaced posteriorly, thus shortening the posterior sagittal diameter in this plane.

The midpelvic plane may also present certain android characteristics. These are:

1. Decreased width of the side walls of the pelvis resulting in a shortened bispinous diameter.

2. Laterally, the male type or narrow sacrosciatic notch is present. The posterior pelvic capacity of the mid- and lower pelvis is therefore decreased and the posterior sagittal diameter in the midpelvic plane abnormally shortened.

The android changes affecting the outlet are:

1. Narrowing of the pubic arch with less arcuate formation of its sides, and a relative shortening of the bituberal diameter.

2. Shortening of the posterior sagittal diameter of the outlet.

These android characteristics may occur at the inlet, midpelvis, or outlet, and in a certain small group of female pelves they may occur in all three portions. These changes may have pronounced obstetrical significance, especially in the completely "android" pelvis. When an individual pelvis shows any android or other significant change, this information is incorporated in the basic classification set down above.

An idea of the distribution of these basic pelvic types in white women may be gained from their incidence in our total cases (800):

> Dolichopellic   type occurred 129 times or 16.12 per cent
> Mesatipellic   type occurred 367 times or 45.88 per cent
> Brachypellic   type occurred 272 times or 34.00 per cent
> Platypellic   type occurred 32 times or 4.00 per cent

We would again call attention to the fact that 62 per cent of this series present pelves whose inlet differs markedly from that described as normal in present-day textbooks on anatomy. To those interested in further studies concerning this question, references to recently published articles are given.[5, 6] Attention also is called to the incidence of the platypellic type in but 4.0 per cent of the series. In many of these pelves the evidence of rachitic influence was notable. It is our feeling that in general the latter type should be regarded as pathologic and therefore considered somewhat differently than the first three groups.

In this group of 200 pelves, the incidence of pelvic type was as follows:

> Dolichopellic,   37 instances or 18.5 per cent
> Mesatipellic,   95 instances or 47.5 per cent
> Brachypellic,   62 instances or 31.0 per cent
> Platypellic,   6 instances or 3.0 per cent

In order to gain some idea concerning the normal range of measurements, certain statistical data in the present series may be interesting. The average measurements for the whole series are:

Inlet:	Anteroposterior	11.6 cm.
	Transverse	12.34 cm.
	Posterior sagittal	4.44 cm.
Midplane:	Anteroposterior	12.25 cm.
	Transverse	10.17 cm.
	Posterior sagittal	5.21 cm.
Outlet:	Transverse	9.05 cm.
	Posterior sagittal	7.84 cm.

Of greater interest are the mean values for the various pelvic types. These are shown in Table I.

TABLE I

	INLET			MIDPLANE			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.53	11.72	5.07	12.55	9.45	5.22	8.95	7.84
Mesatipellic	11.75	12.32	4.48	12.34	10.34	5.23	9.16	7.71
Brachypellic	11.06	12.67	4.15	12.01	10.32	5.23	8.92	8.05
Platypellic	9.0	12.67	2.75	11.67	10.45	4.71	9.12	7.58

Certain conclusions from a survey of this table may be stated. In the dolichopellic type there is a tendency for the anteroposterior-transverse relationship to be maintained throughout the pelvis. In the brachypellic type a similar tendency is maintained, although in a less striking manner. In the platypellic group, the shortened posterior sagittal of the inlet and wide bispinous diameter suggest that rickets plays a role in the etiology of this group. Evidences of the effects of this disease will be found in the sacral contours and sacral positions in many pelves in this group.

For clinical purposes it is useful to establish criteria for the designation of small pelves. Such a designation is necessarily arbitrary and depends upon how far one is willing to stretch the limits of normalcy. However, if "average" pelves may be defined as those lying within the interquartile range, that is, the middle half of all, then small pelves may be defined as those which are measurably smaller. Using the anteroposterior diameter of the inlet as the yardstick, it is found that for each of the first three pelvic types the lower limit of the average group is 0.5 cm. less than the mean for the type. About one-fifth of all pelves are measurably smaller and are, therefore, designated as "small." By this definition small pelves occur with approximately equal frequency in the three pelvic types as indicated below.

Dolichopellic type: Anteroposterior diameter less than 12.0 cm.
Small pelvis 7 instances or 18.9 per cent.
Mesatipellic type: Anteroposterior diameter less than 11.25 cm.
Small pelvis 17 instances or 17.9 per cent.
Brachypellic type: Anteroposterior diameter less than 10.5 cm.
Small pelvis 11 instances or 17.7 per cent.

In further considering the mean measurements given above it may be clinically useful to construct a table based on the lower limits of normal for each measurement. This has been done in the table below. It is our opinion that dimensions smaller than those given for the various diameters should be regarded circumspectly.

TABLE II

	INLET			MIDPELVIS			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.0	11.25	4.5	12.00	9.25	5.0	8.5	7.5
Mesatipellic	11.25	11.75	4.0	11.75	9.75	5.0	8.5	7.5
Brachypellic	10.75	12.25	3.75	11.50	10.00	5.0	8.5	7.5

In considering the clinical relationships of the series (200 pelves), certain interesting facts present themselves. In this group of primiparous patients delivered at term, labor was terminated by operative intervention 36 times, or 18.0 per cent.

A brief analysis of intervention in the series follows:

Dolichopellic type:
1. Small pelvis, contracted midplane and outlet, posterior position, midforceps.
2. Small pelvis, contracted midplane, low forceps.
3. Child 3,920 gm., arrest at outlet, low forceps.
4. Child 4,175 gm., arrest at outlet, low forceps.
5. Prolonged labor, contracted outlet, low forceps.

6. Persistent posterior position, low forceps.
7. Prolonged labor, low forceps.
8. Small pelvis, contracted midpelvis and outlet, low forceps.

Mesatipellic type:

1. Cesarean section, persistent face presentation, contracted outlet.
2. Premature separation of placenta, cesarean section.
3. Arrest of posterior position in midpelvis, midforceps.
4. Contracted midplane, posterior arrest in midpelvis, midforceps.
5. Child 4,180 gm., arrest at outlet, low forceps.
6. Normal pelvic dimensions, arrest at outlet, low forceps.
7. Small pelvis, prolonged labor, low forceps.
8. Normal pelvic dimensions, arrest at outlet, low forceps.
9. Small pelvis, low forceps.
10. Prolonged labor, low forceps.
11. Contracted midpelvis, low forceps.
12. Persistent occipitoposterior, low forceps.
13. Small pelvis, low forceps.
14. Outlet contraction, low forceps.

Brachypellic type:

1. Essential hypertension with dystrophia dystocia syndrome, cesarean section.
2. Premature separation of placenta, cesarean section.
3. Contracted midpelvis, contracted outlet, child 3,935 gm., midforceps.
4. Contracted outlet, transverse arrest, midforceps.
5. Child 4,075 gm., small pelvis, contracted midpelvis, midforceps.
6. Child 3,980 gm., prolonged second stage, midforceps.
7. Child 4,135 gm., contracted midpelvis and outlet, midforceps.
8. Rheumatic heart disease, midforceps.
9. Normal pelvic dimensions, arrest in midpelvis, midforceps.
10. Normal pelvic dimensions, low forceps.
11. Contracted midpelvis, low forceps.
12. Contracted outlet, low forceps.
13. Small pelvis, contracted outlet, low forceps.
14. Contracted midpelvis, arrest at outlet, low forceps.
15. Pulmonary tuberculosis, low forceps.

Platypellic type:

1. Rachitic pelvis, a.p. diam. inlet 6.0 cm., cesarean section.

If we omit outlet or low forceps in this series of 200 deliveries, we find that operative intervention was necessary 15 times, or in 7.5 per cent. The distribution of these 15 operations was as follows:

> Dolichopellic type, 1 operation, or 2.5 per cent
> > Midforceps, 1 instance
> Mesatipellic type, 4 operations, or 4.2 per cent
> > Cesarean section, 2 instances
> > Midforceps, 2 instances
> Brachypellic type, 9 operations, or 14.5 per cent
> > Cesarean section, 2 instances
> > Midforceps, 7 instances
> Platypellic type, 1 operation or 16.6 per cent
> > Cesarean section, 1 instance

As was noted in previous studies, the more serious types of intervention are increasingly necessary in brachypellic or platypellic pelvic types. This re-emphasizes our previous dictum that the most favorable type of pelvic inlet is that which is round or which is elongated anteroposteriorly (mesatipellic or dolichopellic), and not the transversely oval pelvis (brachypellic).

Another criterion in any study of clinical relationships involving the bony pelvis is that concerning prolonged labor. We are well aware that many factors enter into the etiology of this condition, and among these we recognize the following: (I) Unfavorable aspects of the bony birth canal, (II) oversize child, and (III) unfavorable presentation. In this series of 200 labors 38, or 19 per cent, were of twenty-four hours or more duration. In 28, or 73.7 per cent, one or more of the three factors mentioned was present, and in 22, or 57.9 per cent, the pelvis showed abnormal dimensional changes. A brief analysis of these 28 prolonged labors follows:

	Length of Labor	Associated Factors
1.	29½ hr.	Small brachypellic type, contracted outlet, intervention.
2.	41 hr.	Small brachypellic type, child 4,075 gm., intervention.
3.	27 hr.	Dolichopellic type.
4.	27½ hr.	Contracted midpelvis, contracted outlet.
5.	24 hr.	Dolichopellic type, contracted outlet, intervention.
6.	40 hr.	Small mesatipellic type.
7.	32 hr.	Small brachypellic type, contracted midpelvis.
8.	29¼ hr.	Small mesatipellic type.
9.	41½ hr.	Contracted outlet.
10.	28 hr.	Child, 3,980 gm., intervention.
11.	33 hr.	Contracted outlet.
12.	25¾ hr.	Small dolichopellic type.
13.	34½ hr.	Contracted outlet.
14.	24 hr.	Small brachypellic type, contracted outlet, intervention.
15.	30 hr.	Small mesatipellic type, contracted midpelvis intervention.
16.	32 hr.	Contracted outlet.
17.	55 hr.	Contracted midpelvis, contracted outlet, child 4,135 gm., intervention.
18.	31 hr.	Frank breech presentation.
19.	28 hr.	Child 4,090 gm., small mesatipellic type.
20.	48¾ hr.	Child 4,400 gm.
21.	38¼ hr.	Platypellic type, a.p. inlet 9 cm.
22.	33½ hr.	Persistent occipitoposterior, intervention.
23.	50 hr.	Small dolichopellic type, contracted outlet.
24.	70 hr.	Persistent occipitoposterior, intervention.
25.	48 hr.	Small dolichopellic type, contracted outlet, intervention.
26.	30½ hr.	Platypellic type, a.p. inlet 10.0 cm.
27.	48¼ hr.	Contracted midpelvis.
28.	25¾ hr.	Platypellic, a.p. inlet 8.75 cm.

In the table above the incidence of outlet contraction 11 times shows again the importance of this abnormality as a factor in prolonged labor. In 14 instances the pelvic inlet showed dimensions less than normal for the particular type of pelvis and in 5 instances the midplane showed contraction either alone or in combination with contraction elsewhere in the pelvis. In considering both operative intervention and prolonged labor in this series, these findings emphasize the importance of the knowledge which a pelvimetric survey of the whole pelvis furnishes. Furthermore, it seems apparent that unless such a routine survey in primiparous patients is carried out, many significant pelvic changes will remain undiscovered.

In recapitulation we would state:

I. A knowledge of pelvic variations and of the changes that may affect the conformation of the pelvis as a whole or in part is essential for the practice of scientific obstetrics.

II. In order to recognize such changes a knowledge of the diameters and contours of certain pelvic planes is essential. These planes are the plane of the pelvic inlet, the midpelvic plane, and the planes of the pelvic outlet.

III. A dimensional study of the pelvis for obstetric purposes is possible only by roentgen pelvimetry, and simple and inexpensive methods for its performance are herein briefly outlined.

IV. The results of a pelvimetric survey in 200 white women are presented and from the mean diameters a criterion for "small" pelves may be established.

V. An analysis of operative intervention and of prolonged labor in this series shows that abnormal changes in the pelvis must be reckoned as among important etiologic factors.

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CAUDAL ANESTHESIA IN OBSTETRICS*

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IN OUR approach to an ideal obstetric anesthesia, we have been convinced that DeLee has indicated the right direction by emphasizing the advantages of local or regional nerve block. With the hope of contributing some refinements to the technique of local anesthesia in obstetrics, we have undertaken a study of regional nerve block administered by the caudal route.

Caudal or sacral anesthesia is a type of central nerve block and central nerve block anesthesia in general may be classified into two main types: the *subarachnoid block* or so-called *spinal anesthesia* in which the anesthetic is mixed directly with the spinal fluid, and the *epidural anesthesia* in which the anesthetic agent is deposited extradurally and acts on the nerve trunks in the space between the dura and the outer bony canal of the vertebral column. Caudal anesthesia is a type of epidural anesthesia produced by injecting the anesthetic agent through the terminal central sacral hiatus so that it bathes the terminal branches of the spinal cord, and it is generally believed that the agent confines

itself to the region of the cauda equina below the level at which the subarachnoid space, with its spinal fluid, usually terminates. Our investigations indicate that in this type of administration the anesthetic travels to a considerably higher level, particularly if a high caudal technique is employed or the agent is injected with a moderate degree of pressure. Under such conditions we have been able to produce lower abdominal and pelvic anesthesia identical with that produced by Odom (1936) and others who have administered the agent into the epidural space through the second lumbar interspace.

Caudal anesthesia was first conceived and attempted for clinical use by Cathelin, the French urologist, in 1905 and in 1909 it was first used by Stoekel in Germany in the second stage of labor. Subsequently it was taken up by other German investigators (Schlimpert and Schneider, 1910; A. Läwen, 1910; H. Schlimpert, 1911 and 1913), and more recently reports have come from several obstetric clinics in this country (Meeker and Bonar, 1923; Oldham, 1927; Rucker, 1930), particularly regarding the use of this procedure in operative vaginal delivery. These reports have been favorable except that partial or complete failures have ranged from 20 per cent to 30 per cent.

Our interest was stimulated by this question and a series of 200 cases in which caudal anesthesia was used was subjected to critical clinical analysis at The Baltimore City Hospitals, Obstetrical Division. In this clinic all primigravidas are routinely delivered by episiotomy and elective outlet forceps and a considerable number of plastic operations are done immediately post partum. Such routine procedures seemed appropriate for a study of caudal anesthesia and in addition the series comprises a number of the more major obstetric operations.

Our investigation was directed toward the answers to the following questions: Is the procedure safe for both mother and child? Is the anesthesia produced adequate and what are the advantages, if any? What are the effects upon the progress of labor? What is the most efficient agent? and finally, What is the degree of technical difficulty of administration one should expect?

Using 30 c.c. of 1 per cent procaine hydrochloride as a standard, we have attempted to evaluate the advantages, if any, of several different modifications of the technique, including varying strengths and volumes of solution with and without adrenalin. Several of the proprietary local anesthetics were used, for which the manufacturers claim prolonged anesthesia. Accurate observations were recorded concerning the patient's blood pressure and pulse, onset, distribution, character and duration of anesthesia. If the anesthesia was administered during labor, we also recorded data regarding relief from pain, any changes in the character or frequency of uterine contractions and the changes in cervical dilatation or station of the presenting part with, of course, frequent auscultation of the fetal heart beat. Observations were made regarding perineal relaxation and the character of the third stage of labor. Attention was focused for immediate or remote sequelae in the puerperium, such as tonicity of the uterus and bladder, headache and symptoms or signs referable to the local site of injection.

In our first dozen or so cases the procedure was attempted immediately post partum on those patients in whom perineal repair was indicated. We followed the technique of administration with the patient in the lateral decubitus, the method which is almost universally advocated. Thirty cubic centimeters of 1 per cent novocaine were used through a 3-inch 20 gauge, spinal puncture needle. Our results were most discouraging. In our first 15 or 20 attempts, we produced satisfactory anesthesia only several times and occasionally only spotty or unilateral anesthesia. In spite of the fact that in many cases the fluid flowed without resistance and there was no tumefaction of the skin overlying the sacrum, we felt that the sacral canal had not been entered. We were about to abandon the procedure as unreliable when we decided to try the knee-elbow position and use a heavier needle. Our percentage of successful anesthesias immediately increased and shortly thereafter we discovered a maneuver by which we believe we can definitely establish the fact that the needle is in the canal before any solution is injected. With the needle inserted well in the canal and the patient in the knee-elbow position, the needle is partially withdrawn and reinserted with simultaneous downward pressure on the hub of the needle, the tip of the needle can be felt to scrape along the anterior surface of the posterior sacral wall which lies above the needle. If this sign is not elicited, the fluid is not injected, under our more recent procedure. We have had no failures in any case in which this sign was elicited.

Our investigations suggest that 30 c.c. of 1 per cent novocaine with 8 minims of 1:1000 adrenalin solution through a 3½ inch 18 gauge, spinal puncture needle gives results which are the most uniformly reliable, and we have found no advantage in using other agents which are claimed to have a prolonged action. The addition of sodium bicarbonate solution frequently claimed to hasten or prolong the action of novocaine was not confirmed in the few cases in which we have tried it.

TECHNIQUE

The technique of administration and the necessary armamentarium which we now use are as follows: The operating room nurse sets up a sterile tray consisting of a sheet 20 inches by 28 inches, in the center of which is a hole 4½ inches in diameter; a medicine glass containing 30 c.c. of 1 per cent novocaine plus 8 minims of 1:1000 adrenalin; a 10 c.c. Luer syringe; a 25 gauge hypodermic needle; an 18 gauge spinal puncture needle 3½ inches long and a few gauze sponges. The patient is placed in the knee-elbow position so that the back remains horizontal and the area over the sacral hiatus is cleaned with iodine and alcohol. The operator, by palpation, locates the sacral hiatus. This is identified as a horseshoe-shaped notch or as an inverted V-shaped notch usually about 2 cm. above the junction of the coccyx and sacrum. It should be remembered that the sacral hiatus is found in the midline always cephalward from the sacrococcygeal junction. This is a vitally important rule which will prevent possible disastrous results which might occur if the needle were inserted anterior to the body of the sacrum. A small skin wheal is raised just above the sacral hiatus by injecting novocaine through the hypodermic needle and several cubic centimeters of novocaine are then deposited between the skin and the bony sacrum, in the subcutaneous tissues. The needle is then withdrawn and the slight tumefaction caused by the preliminary injection is pressed away with the operator's finger. Otherwise, the location of the sacral hiatus may be obscured. The spinal puncture needle containing a stylet is then introduced through the skin

to the sacral hiatus until bony obstruction is met.   The needle is then placed on an angle of about 10 degrees to 20 degrees with the vertebral column and pressure will now encounter a membranous resistance.   The membrane covering the hiatus is pierced and the needle then meets no resistance as it penetrates the sacral canal.   The needle is inserted to a depth of about 2 inches, then slightly withdrawn and then re-inserted while downward pressure is made on the hub of the needle.   During this maneuver the tip of the needle will be felt to scrape along the overlying bony surface which represents the anterior surface of the posterior sacral wall.   If one desires anesthesia of pelvic viscera, the needle should be inserted 2½ to 3 inches, although occasionally this is not possible in cases where there is a marked curvature of the sacrum and the tip of the needle meets the curving anterior surface of the posterior wall.   The stylet is then withdrawn, and if spinal fluid or blood escapes, the injection should not be done.   If no fluid returns, the empty syringe is attached and the plunger withdrawn to again test for spinal fluid or a steady return of blood.   We frequently suck back a drop or two of blood at this point, but we have found that if there is no steady flow there is no contraindication to injection.   Twenty cubic centimeters of the novocaine mixture is then injected slowly and gently—never under

Fig. 1.—Patient in knee-elbow position with needle partially inserted in sacral canal.   The caudal drape sheet has been omitted so that landmarks may be correlated.

pressure.   It usually flows with very little resistance.   Some patients complain of a cramplike pain in one or both legs at this time but this rarely occurs if the injection is done gently.   If one is preparing for lower abdominal surgery, the total of 30 c.c. should be injected at this level, but if we are interested only in perineal anesthesia, the needle is withdrawn about 1 inch and the remaining 10 c.c. are injected at this point after the usual precautionary tests are made regarding flow of blood or spinal fluid.   This maneuver seems to promote a more rapid onset of perineal anesthesia. Following the complete withdrawal of the needle, the patient is placed flat on her back.   About five minutes later the sphincter reflex disappears, and ten to twenty minutes after the injection, anesthesia appears around the anal region and gradually ascends to a varying height, usually well above the level of the symphysis.   There is a marked relaxation of the anal sphincter and perineal musculature, and following its onset, approximately twenty to thirty minutes following the injection, surgical anesthesia usually lasts about one and one-half hours and disappears from above downward.   There is rarely any sign of motor paralysis although a few of our patients complained of weakness of the legs.   Although many patients complain of numbness of the feet and legs the actual anesthesia usually descends only a short distance down the thighs.

If the anesthesia is administered to a patient in labor, the uterine contractions usually become painless immediately, or several minutes, after the injection.   Fre-

quently the contractions are weaker, of shorter duration, and less frequent for five
or ten minutes following the injection but soon return to their original status except
for the absence of pain. Perineal anesthesia follows in the manner described above
and the contractions continue painlessly until shortly before the perineal anesthesia
begins to wane. As soon as the contractions become painless the patient loses the
urge to bear down and there is usually a dramatic change in her countenance from
one registering anguish to relief and gratitude. If the anesthesia is administered
in the first stage of labor, although painless contractions continue, our experience
indicates that the progress of labor will be arrested until the anesthesia wears off in
most cases. We have found one type of case to be the exception to this rule. In
primigravidas, having hard labor, with the head deep in the pelvis and the cervix thin
but only partially dilated, the anesthetic may be administered and completion of
cervical dilatation and descent of the head to the perineum may be expected, with
complete absence of pain. We have repeated the anesthesia in this type of case to
carry the patient through delivery and repair with gratifying results. Spontaneous
delivery under the anesthesia is, unfortunately, the rare exception, and aside from the
type of case described above, the anesthesia is not administered until the patient is
ready for delivery. Preliminary analgesic drugs are no contraindication to the anes-
thesia, although in our series most of the patients received only preliminary oral
pentobarbital, because we felt that we could more accurately evaluate the anesthesia
under study if the patient received a minimal amount of other drugs which might
mask the picture. The barbiturate analgesia was chosen because of its counteraction
to a possible novocaine toxicity.

<center>RESULTS</center>

In our series of 200 cases we were unable to enter the sacral canal in 14 and
these are classified as complete failures. Eleven of these failures occurred in our
first 45 cases and only 3 in the last 155 attempts. This point indicates that a certain
amount of experience is essential; nevertheless, we believe there is an irreducible
minimum of failures comprising very obese patients and those with an abnormal
sacral contour. In 4 other cases, in which the canal was definitely entered, the
results were only partially satisfactory. In these 4 cases the anesthesia was ad-
ministered ante partum for delivery. All 4 patients experienced complete relief
from pain during contractions but in 2 no perineal anesthesia followed and in the
other 2 only unilateral anesthesia of the perineum was obtained. In the remaining
182 cases the anesthesia was classified as successful although in this group supple-
mentary anesthesia was administered 17 times. Most of these supplementary anes-
thesias were used only during delivery of the head, in the early part of the series,
when we began the operation too soon. At this early date we did not realize that
occasionally the onset of surgical anesthesia is delayed forty or fifty minutes follow-
ing the injection.

<center>TABLE I. 146 CASES RECEIVING ANESTHESIA FOR DELIVERY</center>

	NUMBER	EPISIOTOMY	SUPPLE-MENTARY ANESTHESIA	SCANZONI MANEUVER	HYSTER-OSTOMAT-OMY
Low forceps de-livery	107	103	10		
Midforceps de-livery	14	12	1	2	2
Breech extraction	10	8			
Version and ex-traction	4		3		
Low cervical sec-tion	8		1		
Porro section	1		1		
Spontaneous de-livery.	2				

In 146 of the patients the anesthetic was administered antepartum for the delivery of full-term babies. In 123 of these cases an elective episiotomy was performed. In this group there were 107 low forceps deliveries in which 10 supplementary nitrous oxide anesthesias were administered for delivery of the head. There were 14 mid-forceps deliveries including 2 Scanzoni operations and 2 hysterostomatomy operations. Breech extraction was performed 10 times and internal podalic version and extraction 4 times. In 3 of the version operations deep ether was administered solely for uterine relaxation as we learned from the first version operation that this procedure cannot be done satisfactorily under the regional block alone, because the contractions are not affected. The group also includes 8 low cervical cesarean sections and 1 porro section. In 3 of these laparotomies supplementary anesthesia was used temporarily when the patient complained during peritoneal traction. The 2 remaining patients in the group were multiparas who delivered spontaneously without pain under the regional anesthesia.

TABLE II. 36 CASES RECEIVING ANESTHESIA FOR PROCEDURES OTHER THAN DELIVERY

	NUMBER	SUPPLEMENTARY ANESTHESIA	APPENDECTOMY
Posterior colporrhaphy	16		
Anterior and posterior colporrhaphy	6		
Repair of old rectovaginal fistula	1		
Dilatation of cervix and uterine evacuation	4		
Laparotomy and sterilization	3	1	1
Multiparas in labor	6		

The anesthetic was administered to 36 patients for procedures other than delivery. This group includes 16 posterior colporrhaphies; 6 anterior and posterior colporrhaphies; 1 repair of an old rectovaginal fistula; 4 cases of instrumental dilatation of the cervix and uterine evacuation; 3 laparotomies for sterilization by cornual resection in one of which an appendectomy was also done. The 6 remaining cases were multiparas who received the anesthetic during the first stage of hard labor but labor was arrested until the anesthesia wore off about two hours later, although painless contractions continued during the period of anesthesia.

The average duration of anesthesia in our series was about one hour forty-five minutes from its onset and the addition of adrenalin to the novocaine seems necessary to attain this duration.

There were no maternal deaths in this series and there was 1 stillborn macerated full-term baby in which the fetal heart could not be heard on admission. All other babies delivered in this series were in excellent condition and cried spontaneously. Blood loss accompanying the third stage of labor was minimal and uterine tonicity maximal. One patient had bladder atony during the first twenty-four hours post partum, requiring catheterization twice. We found no untoward symptoms, such as headache, in the puerperium, and there were no signs or symptoms referable to the local site of injection. One-third of the patients manifested some mild vasomotor disturbances immediately following the injection, principally exhibited by a sensation of chilliness and occasionally a sense of anxiety but these symptoms usually disappeared in about five minutes. Most of the patients revealed a rise in pulse rate immediately following the injection, the average rise being 10 beats per minute although this is difficult to evaluate because the carrying out of the procedure with the assumption of the knee-elbow position, per se, probably contributes somewhat. We carried out the procedure on one patient in active labor and injected 30 c.c. of plain normal saline solution and her pulse rose 20 points. One hundred and six patients had no change in blood pressure whereas in 48 patients there was an immediate rise in blood pressure with the average rise in this group being 20 points systolic and 6 points diastolic. In 2 of these patients there was a transient rise in the systolic pressure of 70 points and in another patient a rise of 100 points, without symptoms. We feel that these changes are referable to the adrenalin used in the mixture. In 27 patients the blood pressure fell, with an average fall of 18 points

systolic and 12 points diastolic. In 2 patients there was an alarming fall in pressure with a classical picture of vascular collapse with a fast, thready pulse and marked anxiety. These patients recovered satisfactorily in about fifteen minutes following stimulants and pelvic and perineal anesthesia followed in the usual manner, and they were delivered about one hour later by low forceps and cesarean section, respectively. Both babies were in excellent condition. It seems significant that in both of these cases 2 per cent novocaine was used in doses of 45 c.c. and 60 c.c., respectively, with the usual addition of adrenalin. We feel that penetration of the dural sac or a blood vessel by the needle had been ruled out in these cases before the injection was given. This is a vital point and one must be cautious. In one of our early cases the dural sac was entered and clear spinal fluid dripped from the needle when the stylet was removed, before any fluid was injected. The needle was reinserted at a slightly different angle and no fluid could be withdrawn and then the novocaine solution was injected as usual and anesthesia was produced without event. In retrospect, this seems hazardous and I would hesitate to repeat it. In 1920 Zweifel reported on 4,200 surgical cases operated upon under caudal anesthesia in which 3 deaths occurred shortly after the injection. All 3 deaths were by sudden respiratory failure. Autopsies on 2 of these cases revealed definite evidence that the needle had penetrated the dural sac and the third case was not investigated.

We have endeavored to determine the distribution of the anesthetic agent by injecting 30 c.c. of novocaine colored with methylene blue into the caudal canal of fresh female cadavers, and we have found that with minimal pressure on the syringe the solution distributes itself evenly around the dura in the epidural space up to the eleventh thoracic segment and with only a moderate degree of pressure the solution travels as high as the seventh cervical segment but always extradurally. Walshe (1924) and others have demonstrated that for a comparatively weak novocaine solution the afferent or sensory nerves have a lower threshold for paralysis than motor nerves, and if we accept Cleland's work (1933) which indicates that the afferent nerves from the uterus enter the cord through the eleventh and twelfth thoracic routes in man, then it seems clear that a comparatively weak solution of novocaine distributed evenly in the narrow epidural space as high as the eleventh thoracic segment should produce painless uterine contractions and sensory anesthesia of the lower abdomen and pelvis, without motor paralysis. This is exactly what we find clinically by using the epidural anesthesia in contrast to the usual spinal anesthesia in which the cord is bathed in a much greater volume of a stronger anesthetic solution with the consequent sensory and motor paralysis. In one of the 2 anesthetic accidents with vascular collapse mentioned above, in which 60 c.c. of 2 per cent novocaine were injected under considerable pressure, sensory anesthesia extended up to about 6 cm. above the xiphoid cartilage but there was, however, no evidence of respiratory embarrassment in either of our cases of vascular collapse, and there was no motor paralysis. It seems likely that if a sufficient number of pre-ganglionic sympathetic fibers are subjected to the action of the comparatively strong solution of novocaine as these fibers pass through the epidural space to the lateral sympathetic ganglia, a sympathetic paralysis with a consequent splanchnic dilatation would manifest itself as a vasomotor collapse. We feel, on this basis, that no more than 30 c.c. of a 1 per cent novocaine solution should ever be used.

Recent investigation (H. Koster and others, 1938) indicates that the distribution of an anesthetic agent mixed with the spinal fluid cannot be accurately regulated in spite of the fact that the relative densities are known and the appropriate position is maintained. With the agent confined in the epidural space, however, this contact with the medulla could not occur because the epidural space terminates superiorly at the level of the foramen magnum where the dura fuses with the bone. The administration of an epidural anesthesia through the caudal canal should, therefore, be done with caution and one must be certain that the needle has not penetrated the dural sac before the agent is injected.

To confirm our belief that by using the caudal approach the anesthetic agent confines itself extradurally we first established a sensitive indicator test for the pres-

ence of novocaine in spinal fluid.* We found that spinal fluid withdrawn by lumbar puncture through the third lumbar interspace from patients under surgical anesthesia up to the level of the umbilicus revealed no trace of novocaine if the anesthetic had been administered by the caudal route. On the other hand, spinal fluid withdrawn in a similar manner from patients with the same level of anesthesia administered as a spinal anesthetic was markedly positive to the novocaine test. These same findings held true even though the dose of novocaine, in milligrams, in the epidural anesthesia was thrice that administered spinally.

SUMMARY AND CONCLUSIONS

A clinical study has been made of epidural anesthesia administered by the caudal route, and some refinements have been added to the technique which have enabled us to use this method in a significant number of obstetric cases with successful anesthesia in 91 per cent of the patients.

Our investigations indicate that when administered by the caudal route the anesthetic agent confines itself to the epidural space and travels to a considerably higher level than is generally believed. Our belief has been confirmed by studies on fresh female cadavers which have been injected with colored solutions comparable to those administered clinically. We have also verified the confinement of the agent to the epidural space by finding no trace of the anesthetic in spinal fluid withdrawn by lumbar puncture when anesthesia was present up to the level of the umbilicus.

The advantages of caudal anesthesia are manifold. Pelvic and perineal anesthesia is complete and the uterine contractions become painless and perineal relaxation is marked. Although the urge to bear down disappears there is no motor paralysis and the patient may cooperate by bearing down voluntarily. Uterine tonicity is maximal and thus blood loss is reduced to a minimum. The anesthesia finds its chief usefulness in operative vaginal delivery and spontaneous delivery is the rare exception. The anesthetic may be administered to give an exhausted patient a rest during a protracted labor with gratifying results. In many cases pelvic anesthesia will be sufficiently complete for cesarean section or pelvic laparotomy although, unfortunately, these findings are not constant and cannot be relied upon.

It seems clear that this regional block should be most useful in those cases in which inhalation anesthesia is contraindicated but the widespread routine use of caudal anesthesia would be impracticable and hazardous, because to use the procedure efficiently and safely it is necessary that the operator familiarize himself thoroughly with the technique of administration by training and practice. Many obstetricians could not or would not avail themselves of such an opportunity. The procedure should be of most value in the practiced hand of the

*We are grateful to the Winthrop Chemical Company for submitting the following test: "To a specimen of spinal fluid (a few cubic centimeters) add several small pieces of ice, 2 drops of dilute hydrochloric acid and 2 drops of sodium nitrite (1:10). Add this mixture to a solution containing 0.2 gm. Betanaphthol in a mixture of 3 c.c. of sodium hydroxide T. S. (normal) and 7 c.c. of distilled water. A scarlet-red to orange-red precipitate results." We have found the test sensitive to novocaine concentrations of 15 mg. per cent.

obstetrician who prefers a selective policy of anesthesia and endeavors to adapt the anesthesia to a given patient rather than accommodate the patient to any routine anesthetic.

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THE EFFECT OF PREGNANCY ON GASTRIC SECRETION*

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LOWERED gastric secretion occurring during pregnancy has been designated as one of the possible etiologic factors in the production of anemia during this period.

Nakai[1] (1925), Arzt[2] (1926) and Mason[4] (1931) have reported a high incidence of diminished or absent free HCl during pregnancy. Strauss and Castle[5] (1932) found that 75 per cent of 24 patients did not secrete normal amounts of free HCl or pepsin during more than half of their period of pregnancy. Mettier and Minot[6] (1931) produced evidence suggesting that the acidity of the upper gastrointestinal tract may be of importance in the absorption or utilization of iron compounds.

During the course of recent study of the anemias of pregnancy conducted in Bellevue Hospital[7] (Labate) the state of gastric acidity was investigated. Gastric analyses were performed on 56 pregnant women who entered the hospital during their prenatal period.

METHOD OF STUDY

Pregnant women who were referred to Bellevue Hospital during the prenatal period because of false labor, premature rupture of the membranes, or for observation were subjected to a gastric analysis. The analysis was repeated on the eighth day following delivery. All except 2 of these patients had a secondary anemia on admission to the obstetric ward.

No fluid or food was allowed after 9 P.M. of the night preceding the gastric analysis. A Levine tube which was lubricated with mineral oil was passed to the fundus of the stomach, the fasting contents removed, and 300 c.c. of 7 per cent ethyl alcohol instilled. Extractions of the stomach contents were done at fifteen-minute intervals during the next sixty to eighty minutes. If no free HCl was detected after the second specimen following the test meal, 0.3 mg. of histamine was injected subcutaneously. The quantity of free HCl and total acids of each specimen were determined by titration with Toper's solution and phenolphthalein, respectively.

RESULTS

Fifty-six gastric analyses were performed. Thirty-five of the analyses were done on patients during their last month of pregnancy; 13 analyses were done during the period of pregnancy ranging between thirty-one and thirty-five weeks; 4 between twenty-seven and thirty weeks; 2 during the twentieth week; 1 during the twelfth week; and 1 during the tenth week.

The normal lower limit of free HCl was established at 20 c.c. N/10 acid per 100 c.c. of gastric juice. Patients having a free HCl concentration of less than 20 c.c. N/10 acid per 100 c.c. of gastric juice were considered to have hypochlorhydria. The third group consisted of those patients who showed persistent achlorhydria following the injection of 0.3 mg. of histamine.

Forty-two (75 per cent) of the women studied were found to have normal concentration of free HCl and of total acid in the gastric juice. Nine (16 per cent) possessed less than 20 c.c. of N/10 free HCl per 100 c.c. of gastric juice. Five in this latter group had less than 10 c.c. of N/10 free HCl per 100 c.c. of gastric juice. Five (9.0 per cent) showed posthistamine achlorhydria. One of the 5 patients, showing a complete absence of free HCl, had a macrocytic hyperchromic type of anemia, while the others had a hypochromic anemia.

Two of the patients who were found to have hypochlorhydria during the twentieth and thirty-second week, respectively, developed normal concentration of free HCl later in pregnancy, the former during the thirty-second week and the latter during the thirty-fourth week. A third patient who had normal concentration of free HCl in the twenty-ninth week continued to secrete a normal amount during the thirty-sixth week of pregnancy. A fourth patient persistently showed achlorhydria from the thirty-fourth to the thirty-seventh week of pregnancy, the analysis being performed at weekly intervals.

The group of 42 pregnant women possessing normal gastric acidity had an average maximum concentration of free HCl of 48.88 c.c. and an average maximum total acidity of 59.3 c.c. The range of free HCl in this group was 20 c.c. to 128 c.c. and of the total acid 25.8 c.c. to 142 c.c. Twenty-seven of these patients were in the period of pregnancy ranging between thirty-six and forty weeks; eleven were between thirty-one and thirty-five weeks; 3 between twenty-seven and thirty weeks; and 1 in the twentieth week. The gastric analyses were repeated on 21 of these women in the eighth day post partum. These patients were found to show normal gastric acidity in the post-partum period.

The 9 women with hypochlorhydria had an average maximum free HCl of 10.2 c.c. and an average maximum total acid of 27 c.c. The range of free HCl was 5.4 c.c. to 18 c.c. and of total acid 10 c.c. to 33.6 c.c. Six of these patients were in the period of pregnancy ranging between thirty-six and forty weeks; 2 in the thirty-second week and 1 in the twentieth week. Gastric analyses were repeated on 4 of these patients on the eighth day following delivery. They showed a complete return to normal levels of gastric acidity.

One of the 5 patients showing total posthistamine achlorhydria was in the fortieth week of gestation. A second patient received a gastric analysis during the thirty-sixth week and a third patient during the twenty-eighth week. Two other patients had their gastric analysis on the twelfth and tenth weeks, respectively. Gastric analyses were repeated on the eighth day following delivery on 2 of these women. One showed a return to normal acidity while the other was found to have 10 c.c. of free HCl and 15 c.c. of total acid, per 100 c.c. of gastric juice.

The sample is not sufficiently large among the groups showing anacidity to justify any positive conclusions concerning the effect of gastric acidity on hematopoiesis. Fifty-four of the 56 patients studied were found to have a secondary anemia at the time that the gastric analysis was done. The 42 patients showing normal gastric acidity during the ante-partum period had an average red blood count of 3.60 million and an average hemoglobin (Sahli) of 10.23 gm. The group showing hypochlorhydria had an average red blood count of 3.50 million and an average hemoglobin of 10 gm. The 5 women showing achlorhydria had an average red blood count of 3.10 million and an average hemoglobin of 6.63 gm.

There appears to be some relationship between the gastric acidity and the level of the red blood count and hemoglobin. The drop in the amount of hemoglobin is noticeable in the patients showing absence of free HCl. However, these average figures are misleading because of the small number of cases in the last 2 groups. For example, in the group showing normal acidity the range of the red blood count was 2.67 to 4.1 million and of the hemoglobin 7.5 gm. to 12.77 gm. There were 3 patients in this group who had a red blood count below 3 million, and 4 of these women had a hemoglobin less than 8.7 gm. The 9 women who showed hypochlorhydria had red blood counts ranging from 2.69 to 4.3 million and hemoglobin ranging from 8.0 gm. to 11.6 gm. In the group having achlorhydria the red blood count ranged from 1.35 to 3.9 million and the hemoglobin from 4.9 gm. to 8.7 gm.

An increase in the average red blood count and hemoglobin occurred on the eighth day post partum in all three groups. The rise was most noticeable in the group showing ante-partum achlorhydria, there being an increase of 0.28 million in red blood cells per c.mm. of blood and 2.87 gm. in hemoglobin per 100 c.c. of blood.

DISCUSSION

All except 4 of the 56 patients studied were in the last trimester of pregnancy. Thirty-five were in the last month of pregnancy. Perhaps this may account for the large number (75.0 per cent) of the patients showing normal gastric acidity. Strauss and Castle[5] in a study of gastric secretion on 24 patients during pregnancy reported a 50 per cent decline in maximum free acidity from the third to the sixth month with a rise in the last month to the level observed in the third month. They found that 18 of these patients showed hypochlorhydria during most of the period of pregnancy and only 6 were within the normal range of gastric acidity.

Nakai[1] obtained an average free acidity of 22 c.c. during the first half and 27 c.c. during the second half of pregnancy among 14 patients. Arzt[2, 3] found anacidity in 5 pregnant women during the first trimester and an average of 11 c.c. N/10 HCl per 100 c.c. of gastric juice in 13 others. In a later investigation in which he studied 50 pregnant women, he found 29 lacking free HCl during the first trimester, 6 of whom showed an average of 11 c.c. in the last trimester. Mason[4] studying 4 patients reported hypochlorhydria in 2 with an average of 8 c.c. during the first trimester.

Mettier and Minot[6] made observations which suggest that anemia may result from failure, over a prolonged period of time, in adjustment of the contents of the upper gastrointestinal tract to a pH more suitable for iron utilization. Their findings indicate that iron compounds are absorbed more readily from the gastrointestinal tract or are utilized more readily for blood formation when administered with an acid than with alkaline meals.

Strauss and Castle[8] made observations which suggested to them that the hypochromic anemias of pregnancy are due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of fetal demands for blood building materials. The macrocytic anemias of pregnancy they thought to be due to a temporary lack in the gastric juice of the specific intrinsic factor which has been shown to be absent from the gastric juice of patients with Addisonian pernicious anemia in relapse.

At present this report indicates that no precise correlation should be made between the acidity of the upper gastrointestinal tract and the development of the secondary anemias of pregnancy. Fifty-four of the patients studied were found to have a secondary anemia at the time that the gastric analyses were done during the ante-partum period. One

patient developed a hyperchromic macrocytic anemia in the twenty-eighth week of gestation. She was found to have achlorhydria. Recovery was complete during the post-partum period with return of the gastric acidity to normal. Four other patients having achlorhydria had hypochromic anemias of pregnancy. Lowered gastric acidity may accentuate an anemia which results from factors other than altered gastric acidity, by making difficult the absorption or utilization of iron. This would explain the average lower levels of the red blood count and hemoglobin found in the pregnant women showing hypochlorhydria and achlorhydria.

SUMMARY AND CONCLUSIONS

1. Gastric analyses were done on 56 women during pregnancy.

2. Forty-two (75.0 per cent) showed normal gastric acidity. Nine (16.0 per cent) showed hypochlorhydria; and 5 (9.0 per cent) showed complete post-histamine achlorhydria.

3. Fifty-two of the patients studied were in the last trimester of pregnancy, 35 of these being in the last month of pregnancy. Two patients were in the fifth month of pregnancy, 1 was in the twelfth week, and 1 in the tenth week.

4. The average red blood count and hemoglobin showed a decrease as the gastric acidity diminished. This, however, should not be taken as proof that the altered gastric acidity is the main factor in the production of the hypochromic anemias of pregnancy.

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Human spermatozoa are capable of reactivation in spite of exposure to extremely low temperatures. A certain definite percentage of those so exposed resume their normal motility when the temperature is returned to normal. The author exposed spermatozoa to temperatures of minus 196° C. for periods varying from four to fifty-two hours, by means of liquid nitrogen. Others were kept at minus 79° C. for forty days and a final group were exposed to minus 269.5° C. by means of liquid helium for five-hour periods. Following each of these experiments a small percentage of spermatozoa became actively motile again.

RALPH A. REIS.

RUPTURE OF PELVIC INFLAMMATORY MASSES INTO THE URINARY BLADDER

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O N THE Gynecological Service of Harlem Hospital, pelvic inflammatory diseases comprise more than 60 per cent of the admissions. When one considers the frequency of inflammatory masses and tubo-ovarian abscesses, it seems remarkable that more of these do not rupture into the bladder and produce a fistulous communication. Rupture of a pyosalpinx into the urinary bladder has been reported only once before from this hospital.[1]

PATHOLOGY

If the pathologic anatomy of the infected tubes is taken into consideration, one can readily understand why rupture of a pus tube into the bladder occurs so rarely. Most tubal inflammatory masses lie behind the uterus. It is only rarely that a pus tube is observed lying on top, in front of the uterus, or adherent to the anterior abdominal wall or bladder. In these cases, the original infection, usually gonorrheal, occurs while the tube is anterior to the uterus, and the pus exuding from the fimbriated end of the tube causes a localized peritonitis. As a result, the fimbriated end of the tube becomes adherent to the bladder in the same way that it may become adherent to the ovary or broad ligament. If the infection "clears up," nothing further occurs except adhesion of the fimbriated end of the tube to the bladder. If re-infection occurs, and a pus tube forms, the bladder wall becomes part of the abscess wall. The inflammatory process may invade the bladder wall itself, producing a tubovesical abscess which under certain conditions may rupture into the bladder.

Another type of pelvic inflammatory mass which may rupture into the bladder is found in the postabortal parametric cellulitis. Here the infection leaves the uterus via the lymphatics of the broad ligament forming an exudate between the layers of the broad ligament or the cellulitis may go posteriorly and infringe upon the rectum, or anteriorly and involve the bladder wall. If it extends anteriorly, and the abscess infringes on the bladder, it may ultimately rupture into the bladder.[2]

According to Huet all pelvic inflammatory masses open into the bladder in one of two ways. (1) Rupture. This occurs in the "cold" type when there is a large abscess in the subacute or chronic stage, with marked thinning of the bladder wall. Rupture into the bladder occurs as a result of trauma, a direct blow on the abdomen, coitus, or a too rough gynecologic examination. (2) Perforation. This occurs with an acute abscess, the fistula being established by the gradual extension of the inflammatory process from the abscess cavity, through the various coats of the bladder wall until, finally, the mucous membrane gives way, and there is drainage of the abscess into the bladder.

PREMONITORY SYMPTOMS

These are difficult to define. As a rule most patients with pelvic inflammatory disease (except postabortal parametritis) present urinary symptoms such as urinary frequency, urgency, burning, etc. However, should a patient with pelvic inflammatory disease have involvement of the bladder wall, it is very difficult to state whether

the bladder symptoms are due to the basic gynecologic condition or to the involvement of the bladder wall.   Associated chills and high fever may be present due to the underlying pelvic pathology.

The severity of the local symptoms varies with the extent and location of the involvement of the bladder wall; the bladder is very resistant to contiguous inflammatory conditions.   As a result, the exudate may not invade the bladder cavity itself, it may only invade the bladder wall to the mucosa with the production of severe urinary symptoms.   The closer the inflammatory exudate to the bladder base, neck, and trigone, the more severe are the symptoms.   Intravesical evidence of the perivesical inflammation varies with the type and extent of the latter.   If frequent investigations of the urinary tract are carried out, and careful examinations of the urine made, an impending rupture of a perivesical abscess into the bladder may occasionally be anticipated.

Before rupture takes place there is usually an infiltration of the bladder wall, with a gradual diffusion of the exudate from the outer coats through to the mucosa with marked edema of the latter.   If a patient, with a pelvic inflammatory mass, shows a localized area of bullous edema on the roof or posterior wall of the bladder, the possibility of impending rupture should be considered.

SYMPTOMS OF RUPTURE

The onset of the rupture may be so insidious that there is barely any change of symptoms from those of the prodromal irritative cystitis, to the actual cystitis caused by the pus.   On the other hand, it may be very acute; the patient may have voided a clear urine and five minutes later, without experiencing any pain, she may have the desire to urinate again and pass several ounces of pure pus.   The patients may experience a feeling of ``something giving away.''

SYMPTOMS AND SIGNS OF ASSOCIATED CONDITIONS

The symptoms of the pre-existing pelvic inflammatory disease, salpingitis, or postabortal cellulitis, may vary with the extent and acuteness, or chronicity of the underlying pathology.   Usually these patients are acutely ill with high temperature and chills.   The pelvic abscess itself is usually quite large, painful, and extremely tender.

DIAGNOSIS

The sudden onset of cystitis, with large quantities of pus in a urine which had previously been fairly clear, in a patient acutely ill with a pelvic inflammatory disease, whose temperature descends by crisis, suggests the diagnosis.   Cystoscopic examination at this time establishes the diagnosis.   The bladder picture seen in these cases is quite typical.   The bladder is filled with large or stringy pieces of pus, so dense that repeated irrigations are necessary before clear visualization can be obtained.   (An important differential point is that the flocculent shreds of pus seen in the bladder in this type of cystitis are too large to have been ejected from the ureters.)   The area surrounding the fistula is usually the site of a bullous edema, a cobble-stone arrangement of very small, translucent, or reddish cysts, the cysts varying in size from a millimeter to several centimeters.   From the center of this edematous area, strings of yellowish or whitish exudate may be seen dripping into the bladder, intermittently or continuously.   Pressure on the inflammatory mass, through the lower abdomen causes an increase in the flow of pus.   Visualization of the actual perforation is difficult, as this lies deep in a craterlike area caused by the edema and hyperanemia of the surrounding tissue.   The entire picture is that of an inverted volcano.   In cases of rupture of a cold abscess the fistula may be visualized because of the absence of edema and signs of acute inflammation in the bladder wall.   It has been described as a pin-point opening, surrounded by a small area of hyperemia.

Various authors have suggested the injection of lipiodol or dyes into the area of suppuration as a means of confirmation of the diagnosis.   The use of lipiodol, or other contrast medium, to establish the diagnosis seems fraught with danger,

REVIEW OF CASE HISTORIES FROM THE LITERATURE

Di Palma and Stark, in 1929, made a comprehensive survey of the literature up to that time with abstracts of 33 cases. The following cases have been gathered from the literature since then

AUTHOR	AGE	HISTORY	GYNECOLOGIC FINDINGS	TIME OF RUPTURE	CYSTOSCOPY	TREATMENT	RESULT
Molfino Boero Chacon	19	Attempted induced abortion with catheter 5 days prior to admission	Bilateral adnexal masses	5 weeks after admission	11 weeks after admission ureteral edema near left ureteral orifice with healed scar in center	Conservative	Cured
Molfino Boero Chacon	45	Attempted induced abortion with catheter 3 days prior to admission	Large left adnexal mass	6 days after admission	Small deep opening surrounded by an area of edema 1 cm. above left urethral orifice	Conservative	Cured
Caporale		Left lower quadrant mass and pain since delivery several years ago			Walnut size area of bulbous edema on the body of bladder from center of which exuded pus	Conservative	Cured
Aes	31	3 year history of P.I.D. following delivery	Large mass right adnexa	3 months after admission urine suddenly contained foul blood and pus		Conservative	Cured
Aes	34	Urinary symptoms following spontaneous miscarriage	Left parametrial mass			Conservative	Cured
Aes	24	Abdominal pain and fever following dilatation of the cervix—3 months prior to admission	Bilateral masses	4 days after admission gross pyuria occurred		Conservative	Cured
Aes	39	Chills, fever, abdominal pain dysuria—6 weeks	Bilateral moderately large adnexal masses		Localized area of edema posterior bladder wall abdominal pressure caused pus to exude from center of this area	Conservative	Cured
Aes	24	Fever and urinary symptoms following spontaneous abortion 1 year ago	Fair-sized mass fixed to right pelvic wall		Entire bladder wall congested, area of edema and perforation behind the right ureter	Conservative	Cured

Name	Age	Symptoms / History	Mass	Pyuria	Findings	Treatment	Result
Babies	31	Right lower quadrant pain, fever, urinary frequency	Adnexal mass right lower quadrant	Few days after admission pyuria with remission of symptoms		Conservative	Cured
Babies	30	Chills, fever following an induced abortion 3 years ago	Left adnexal mass, myoma of uterus		At junction of fundus and posterior wall of bladder area of bulbous edema. Abdominal pressure caused pus to exude in this region	1. Hysterectomy 2. Left salpingo-oophorectomy 3. Closure of bladder fistulas	Cured
Babies	20	Pain in left kidney region and abdomen; chills, fever following delivery three months ago	Bilateral parametritis		Right side of fundus there was an area of edema, the size of a walnut from which exuded pus	Conservative	
Fagerstrom	28	11 year history of P.I.D. following induced abortion—past 6 months urinary symptoms with pyuria	Right tubo-ovarian abscess	6 months prior to admission	Papillary tumor on the posterior wall of the bladder from which dropped thick yellow pus	1. Right salpingo-oophorectomy 2. Closure of bladder fistulas	Cured
Ottow		Normal delivery 6 months prior to admission	Bilateral adnexal masses		Area of bulbous edema on posterior wall of bladder from which intermittent ejections of pus occurred	1. Hysterectomy 2. Bilateral salpingo-oophorectomy 3. Closure of bladder fistulas	Cured
Ottow	48	Recurrent pain, fever and pyuria	Bilateral adnexal masses		Bulbous edema with a small fistula above right ureter, subsequently perforation into ureter occurred	Refused operation	Cured
Sorrentino	28	Recurrent pain, fever and urinary tenesmus	Very tender mass the size of a fist in right fornix	Shortly before admission	Large fistulous opening on right lateral wall of bladder covered with exudate	1. Appendectomy 2. Right salpingo-oophorectomy 3. Resection bladder wall	Cured
Sofronov (6 cases)		Reports 6 cases, 5 following postabortal parametritis and one following gonorrheal pyosalpinx. 4 patients were treated conservatively, one patient by anterior colpotomy and one patient by laparotomy and colpotomy.					

in the face of an active suppurative process. Acute exacerbation of the infection may frequently follow this procedure. The history and the cystoscopic picture should be sufficiently clear to establish the diagnosis without further aid.

PROGNOSIS

The prognosis is favorable but the course may be protracted, ranging from one to six months, depending to a large extent upon the underlying pathology and how rapidly it recedes, either spontaneously, under local treatment, or through surgical intervention. In those instances where a mortality has been reported, as a rule, it has been due, not to the rupture of the abscess into the bladder but to the severity of the underlying pathology.

TREATMENT

Treatment is divided into three parts:

A. Prophylaxis.—

All patients presenting pelvic masses associated with urinary symptoms should be carefully observed and have repeated cystoscopic and urine examinations. When cystoscopic evidence of impending rupture presents itself, active treatment directed to the underlying pathology should be undertaken to prevent rupture (surgical treatment).

B. Active Treatment.—

1. Local.

2. General:

The treatment of the bladder following rupture of the abscess is the same as that used in acute cystitis. An indwelling catheter may be used until the acute symptoms have subsided to avoid the necessity of too frequent catheterization. The bladder is irrigated with the usual urinary antiseptics; silver nitrate 1:4000; boric acid, 4 per cent; acriflavine, 1:5000; and instillations of 10 per cent argyrol; or a combination of any of these. It is very important to start the bladder irrigations early as the bladder rapidly becomes filled with pure pus, and the possibility of reflux drainage into the kidney pelves must be considered. Early drainage of the abscess, should be carried out either by colpotomy or extraperitoneal incision. The opening in the original abscess must be free so that the pus will flow through the drainage tract rather than into the bladder.

General treatment consists of rest in bed, douches, short wave therapy, Elliot therapy, sedatives.

C. Late Treatment.—

This consists in the removal of the underlying infection. In postabortal infection the exudate may subside spontaneously or may require extraperitoneal drainage. If due to pus tubes, these may be removed when Simpson's rules are complied with (absence of temperature for three weeks, etc.). When these tubes are removed, as a rule it is not necessary to repair the bladder at the site of rupture. However, in several cases reported from the literature, the location of the bladder communication was found and closed during the laparotomy for the removal of the adnexal masses. This has not been necessary in any of our cases.

PERSONAL CASES

CASE 1.—L. J., aged 33, colored, para 0, gravida 0, was admitted to Harlem Hospital, April 10, 1936, with a three weeks' history of constant pain in the left lower quadrant, accompanied by high temperature and chills. She had marked dysuria for two weeks previous to admission and a severe chill the night before. Patient appeared acutely ill. Temperature was 103° F., pulse, 152. Abdomen was distended and rigid, and a hard, irregularly nodular mass was palpated in the lower abdomen, extending to just below the umbilicus. Vaginal examination revealed a large mass filling the pelvis and lower abdomen. Urinalysis showed many clumps of pus cells,

about 100 white blood cells per high power field, and albumin, three-plus. Blood count: Hb, 55 per cent; red blood count, 3,210,000; white blood count, 34,700; Polymorphonuclears, 90 per cent; stools: negative; Aschheim-Zondek, negative; blood Kahn, three-plus. Blood cultures were repeatedly negative.

A diagnosis of fibroid uterus and left pyosalpinx was made. The patient was given daily bladder irrigations of 4 per cent boric acid, and instillations of 10 per cent argyrol. Seven and a half grains of urotropin, 5 gr. of acid sodium phosphate, and 15 min. T.I.D. tincture of hyoscyamus were administered orally. During the next three weeks she was given three blood transfusions of 500 c.c. each. The temperature varied from 100 to 103. At the end of this time the patient's condition was much improved. Spontaneous rupture of the inflammatory mass into the bladder must have occurred toward the end of the second week in the hospital, as the report of the urine shows there was a marked increase of pus in the urine for several days with an improvement in the patient's general condition.

Cystoscopy was deferred until May 7. A No. 24 cystoscope was easily introduced. Bladder capacity was limited (about 150 c.c.). The bladder contained many flocculi and a tremendous amount of exudate, with particles that were too large to have come through the ureter. The urethral orifices were normal in appearance and location. There was a general hyperemia of the entire bladder mucosa with dimming of the blood vessels. A large area of bullous edema was seen at the junction of the roof and the posterior wall of the bladder, with considerable bulging of that region into the bladder. After thorough irrigation pus was found to be dripping from this area to the floor of the bladder, just posterior to the trigone. Otherwise the roof and sides of the bladder were normal. Indigo carmine injected intravenously appeared in normal time and concentration from both ureters.

Diagnosis.—Acute cystitis. Rupture of pyosalpinx into the bladder.

Examination on July 1, 1936, showed the mass to be three fingerbreadths below the umbilicus. A large left adnexal mass was made out vaginally. The right adnexa felt normal. On July 22, the one hundred and fourth day of hospitalization, the patient was discharged to return at a future date for surgery. Temperature was normal for over a week previous to discharge. Urine at the time of discharge showed a few pus clumps and only 10 white blood counts per high power field.

CASE 2.—J. S., colored, 33 years of age, para i, gravida i, was admitted to Harlem Hospital on April 3, 1936, with a three months' history of severe generalized abdominal pain.

Patient appeared acutely ill. Temperature 106.6° F.; pulse, 134. The abdomen was distended, tender, and moderately rigid, particularly in the right lower quadrant. A large mass could be palpated in the lower abdomen extending up to the umbilicus. Vaginal examination revealed a thick, creamy discharge, and verified the tender mass filling the entire pelvis. It was impossible to outline the uterus. Urine examination, few white blood cells per high power field. Albumin three-plus. Blood count: Hb, 55 per cent; red blood count, 4,500,000; white blood count, 8,650.

A diagnosis of a ruptured or leaking pyosalpinx was made. The patient was given an infusion of 1,000 c.c. of 5 per cent glucose in saline and a Harris drip. For a month following admission, patient showed signs of lower abdominal peritonitis, but at the end of this time, temperature had receded to 102° F. and pulse to 120. On May 7, 1936, her urine suddenly showed a marked increase in white blood cells with large clumps and shreds of pus. On May 27 urinary symptoms were diminished, although the urine still showed large amounts of pus. Cystoscopy on this date was reported as follows:

Caliber of urethra very small. Smallest Hanks dilator, No. 11, could not be inserted. Under evipal anesthesia, the urethra was dilated to admit a No. 18 dilator. A No. 24 cystoscope was then easily introduced but had to be depressed downward and backward, with the eye piece upward and almost against the left thigh, at an angle of 90 degrees, as the bladder was markedly distorted and pushed to the right. The entire bladder mucosa was edematous and hyperemic, neither the blood vessels, trigone, nor ureteral orifices could be made out. On the floor of the bladder, posteriorly, there was a localized mound of white which appeared to be pus. There was a bulging area of bullous edema on the roof of the bladder; in the center of this

area there was an old blood clot, apparently covering a small excavation. Due to the tremendous amount of purulent flocculi visibility was greatly impaired. After thorough irrigation, it became apparent that the source of the pus on the floor of the bladder was from a fistulous opening in the roof of the bladder. Strings of pus, were seen hanging from the roof and constantly dripping to the floor of the bladder.

Diagnosis.—Rupture of a pyosalpinx into the bladder.

Colpotomy (anterior) was performed the following day. A large soft, yielding mass was felt in the anterior cul-de-sac, extending to the right side. Incision with scissors was made at the cervicovaginal junction anteriorly. The anterior vaginal mucosa was separated from the cervix. Separation of a plane of cleavage in this space opened into an abscess from which almost 350 c.c. of very foul-smelling pus escaped. A self-retaining catheter was inserted into the bladder, and two rubber drains into the abscess cavity. Three days after operation the patient's temperature became normal and there was a marked diminution in symptoms.

On June 15, 1936, seventy-three days after admission, patient was discharged at her own request. At this time the urine still showed a few pus clumps, the temperature was normal, but a mass was still present in the center of the abdomen.

The patient was seen again on July 8, 1937, at which time her only complaint was incontinence. Cystoscopy on this date showed a small opening about the size of a pea just posterior to the interureteric ridge in the midline. The rest of the bladder was apparently normal. Attempt to pass a ureteral catheter through this opening was unsuccessful. Indigo carmine, intravenously, appeared in five minutes in the vagina, the source of which was definitely from the old anterior colpotomy wound.

CASE 3.—R. B., white, 32 years old, married fourteen years, para i, gravida 3, was admitted to French Hospital on Aug. 1, 1938, with a four months' history of severe pain in right lower quadrant following an abortion.

The patient appeared acutely ill, temperature 103° F., pulse 130. There were marked tenderness and slight rigidity in the right lower quadrant.

Vaginal examination: External genitalia normal. Cervix in axis of vagina. Uterus normal size, and in good position. A large fluctuant mass filled the right anterior fornix. Posterior cul-de-sac and left fornix clear. Laboratory findings: Urine negative except for few white blood cells. Repeated blood cultures were sterile. Blood count: red blood count, 3,350,000; white blood count, 11,600; polymorphonuclears, 70 per cent; Hb, 60 per cent; lymphocytes, 30 per cent.

Temperature fluctuated from 99 to 102° F. until operation on August 18.

Preoperative Diagnosis.—Pelvic abscess. Parametrial postabortal. Just prior to doing a colpotomy the patient was catheterized and pure pus was obtained from the bladder. An anterior colpotomy was performed, opening an abscess between the bladder and the lateral pelvic wall. Several ounces of pus was obtained. A drainage tube and one piece of vaginal packing were inserted. Smears from the abscess showed pus cells, and gram-negative diplococci. Culture showed gram-positive bacilli and diplococci. The immediate preoperative catheterized urine examination was very significant as a urine examined earlier that day on the ward was negative. It was obvious that the abscess had ruptured into the bladder while the patient was being taken from the ward to the operating room. Within a week, following the colpotomy the urine became fairly clear though still containing considerable pus cells and within two weeks, only a few pus cells were found per high power field.

Temperature rose to 105° F. following operation but readily receded, and the patient was discharged in three weeks with a negative urine and a mass still present in the right fornix.

CONCLUSIONS

1 Spontaneous rupture of pyosalpinx or pelvic abscess into the bladder occurs.

2. The symptoms and signs are usually masked by the underlying pathology. Rupture of a pelvic inflammatory mass into the bladder is usually shown by the sudden appearance, or marked increase of pus in

the urine with severe urinary symptoms such as urinary frequency, burning, and tenesmus. Such symptoms are very significant if followed by improvement in the patient's condition and recession of temperature.

3. Cystoscopy establishes the diagnosis, revealing a localized area of bullous edema, from the center of which pus exudes.

4. The fistula usually heals spontaneously with recession of the mass by medical treatment or surgical intervention.

5. Gynecologic cases with a pelvic mass should have a routine investigation of the genitourinary tract, including cystoscopy, as the presence of local edema of the bladder mucosa from contiguous inflammatory mass may be a premonitory sign of perforation.

6. Three cases of rupture of a pelvic infection into the urinary bladder with a collection of 21 cases from the literature are reported.

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THE UTERUS ARCUATUS*

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WE MAY define uterus arcuatus as that form of bicornuate uterus in which the normal fusion of the two horns in embryonic life stopped just short of completion forming an organ which in the nonpregnant state can with difficulty be differentiated from a normal uterus but which, when pregnant, exhibits marked irregularities of contour.

The most extreme grades of bicornuate uteri are for the most part anatomic curiosities which rarely have clinical significance. If such uteri contain a pregnancy they usually abort the product of conception, or carry it through and present an indication for cesarean section at term, because of malposition or dystocia or both. In such cases repetition of pregnancy in the future is avoided by sterilization, either by hysterectomy or salpingectomy. The recognition of these extreme grades of bicornuate uterus is relatively easy from careful clinical observation, since a marked degree of deformity usually leads to signs and symptoms quite different from those of normal pregnancy.

There is, however, a much more common type of bicornuate uterus (uterus arcuatus), which frequently gives rise to obstetric complications

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of the gravest concern. Discussions on this subject are conspicuous by their absence in the literature. Bumm[1] in his textbook on obstetrics devotes one sentence to the subject. He says, ''Labor in this type of uterus is apt to be complicated.'' DeLee,[2] Williams,[3] Bland[4] and Schumann[5] all mention the deformity but do not discuss adequately its clinical significance. In 1924 I[6] called attention to this subject in a paper read at a meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. At that time I stressed the dangers to the baby that might occur, especially during labor. I described the complications in the relatively few cases I had observed and made certain recommendations based on these observations. Since that time we have carefully observed and recorded the labors of a considerable number of women who have presented this abnormality, and wish to present the results of this study.

It should be noted that at one stage of development all uteri are bicornuate. The normal process of fusion of the two horns to form a pear-shaped organ results, when carried to completion, in the formation of a uterus well adapted to carry out its part in the process of reproduction. When the fusion is interfered with, the result is an inferior organ frequently incapable of performing this duty normally. The functional deficiency varies directly with the degree of deformity.

The etiology of this deformity is totally unknown. What influences the arrest in development of the uterus can only be surmised. Since it is highly probable that the development, growth, and functional activity of the uterus are so directly under the influence of the hormones, it would seem that a failure of the body to supply these hormones in the proper amount and at the proper time in intrauterine life might be the principal cause responsible for the improper fusion of the two halves of the uterus, as well as for other developmental deficiencies in the organ that may explain certain clinical phenomena mentioned later.

Clinically, the condition can be diagnosed in the early weeks of pregnancy. As a rule the uterus will appear larger on one side than the other. Frequently the development of the body of the uterus will be eccentric. One side will grow much faster and be softer than the other. The smaller horn may present at term merely as a nodule on the surface of the hypertrophied side containing the pregnancy, and has often been mistaken for a fibroid. This is frequently associated with lateral deviation of the body of the uterus toward the side of the hypertrophied horn. Often seven-eighths of the uterus will be found to the right or left of the midline. In other cases the two sides of the uterus seem to hypertrophy at about the same rate and at term the fundus of the uterus instead of being rounded, presents a groove or notch on its upper aspect with the horns on each side. The width of the fundus in these cases is greater than normal.

I have a very distinct clinical impression, not however based on actual measurements, that the thickness of the uterine wall and lower uterine segment is less than in normal uteri. This impression is partially created by the weak character of the pains so frequently seen in these cases and partially by feeling the fetal parts unusually clearly

through the abdominal and uterine walls. In some cases at cesarean section, certain parts of the uterine wall especially over the cornua seemed to be unusually thin before and after opening the uterus. The same impression was gained in some cases in which it was necessary to remove the placenta manually because of an abnormal third stage. It is probable also that these uteri have abnormalities of the blood supply and these combined with the abnormal musculature may explain certain clinical observations, especially intrauterine asphyxia.

The more marked grades of bicornuate uterus frequently present abnormalities of the cervix or vagina. Patients with uterus arcuatus rarely present these deformities.

Diagnosis.—The diagnosis of this abnormality is usually easy when the physician is familiar with the condition. The main reason for failure in diagnosis is unfamiliarity with the clinical manifestations. Early in pregnancy, up to the third month, the above-mentioned difference in size of the two sides of the uterus will nearly always be noticeable. That containing the growing fetus may be two to three times as large as the other. The consistency is also markedly changed, the side of the uterus containing the developing fetus will be much softer and feel more cystic. In some cases a distinct groove may be felt between the right and left sides of the uterus. If the softening is more marked in the region of one cornua, the possibility of an interstitial ectopic pregnancy is raised in the mind of the examiner. The differential diagnosis by physical examination may be impossible until symptoms of rupture appear.

Later in the pregnancy, the diagnosis is strongly suggested by the shape and position of the uterus. Not infrequently the contour of the uterus will be roughly heart shaped. It is much broader across the top and the size of the horns may be approximately equal or one may be considerably larger than the other. When the latter condition is present, the uterus assumes an oblique position in the abdomen and often a large portion of the organ will be to the right or left of the midline. The lateral edge of the uterus may extend beyond the crest of the ileum in some cases.

On palpating the fetus it will be found in many cases to be in an obliquely transverse presentation; when this is true in a primipara it is practically pathognomonic. The presenting part may be found in the right or left iliac fossa and attempts to move it over to the midline and to engage it by the Mueller impression are usually unsuccessful.

Vaginal examination reveals the presenting part to be very high and the characteristic mass of the head or breech may be absent from the inlet. In those cases in which the baby is presenting by the breech, external version is difficult or impossible after the eighth month. X-ray picture confirms the clinical findings as to the presentation and position. Cephalopelvic disproportion can be estimated. However, the shape of the uterus itself is usually not easily appreciable by study of the x-ray plate.

The heart tones show a curious irregularity. In many cases as one listens over a period of a minute or more an irregularity of rate will be clearly distinguished. It may be 120 or 130 at the beginning of auscul-

tation and rise to 150 to 170 for a quarter of a minute or more and then without apparent cause slow down to 100 to 110. When labor sets in, this irregularity may become accentuated in some cases and not in others. It also may be much more noticeable in the first stage of labor than in the second; when one would expect in normal cases the heart tones to become weak, rapid, and irregular, we find that they may steady down and be normal in rate and rhythm. One of the dangers of the condition is that the heart tones may stop entirely as has happened in some of our cases early in the first stage of labor. In thin women during labor, the abnormal contour of the uterus may be clearly visible when the uterus contracts, and even in stout women it can be distinctly made out by palpation. The same is true during Braxton Hicks contractions before labor begins and in the third stage of labor. A few hours after delivery the uterus assumes a more rounded contour and the bicornuate nature cannot be so easily appreciated.

The condition must be differentiated from fibroids of the uterus, especially pregnancy in the fibroid uterus. The fibroid is usually firmer than the unsoftened side of the uterus in early pregnancy for which it may be mistaken. Usually one can detect other fibroids in the uterus besides the one which might simulate the pregnant horn. The enlargement of the uterus caused by the fibroid is usually much less symmetrical. The presumptive signs of pregnancy and the Aschheim-Zondek test are valuable in differentiation.

The soft cystic pregnant horn of the uterus may simulate an ovarian cyst and the unsoftened side of the uterus be interpreted as a nonpregnant uterus. In such a case the amenorrhea of pregnancy might be ascribed to disturbances of ovarian hormone secretion. The mistake would rarely be made by a trained examiner but might be made by a general practitioner.

Clinical Course.—The clinical course of labor in patients who present this abnormality of the uterus differs markedly in individual cases. It is this circumstance which makes the management of these labors difficult to outline.

The onset of labor in a small percentage of cases is premature from a few weeks to two or three months. In a somewhat larger group, however, there is a definite tendency to postmaturity, varying from a few days to a week or more. This may be due, in part at least, to the failure in many cases of the presenting part to engage normally at term. This in turn is due to the obliquely transverse presentation of the fetus and to the deficiency in development of the uterine muscle. Induction of labor is frequently necessary, and the response may be weak and unsatisfactory.

When labor starts spontaneously, the pains are often weak and irregular and a slow course of labor may be anticipated. However, in some cases apparently the resistance of the cervix is proportionately less than the decrease in contracting power of the uterine muscle and as a result the first stage of labor may terminate more rapidly than normally.

The second stage also may complete itself in normal time but there is a definite tendency to primary uterine inertia or to secondary inertia due to malposition.

The heart tones in such cases are frequently abnormal in rate and rhythm. Not infrequently they are found to be from 160 to 170 before labor starts or in the first stage when pressure on the fetal head or the usual causes of fetal exhaustion during labor can be disregarded as a cause. The explanation of this finding is not easy. We have felt that it is probably best explained by assuming that the deficiency in muscular development of the uterus with corresponding abnormalities in the blood supply to the placental site, may be important factors. It is also possible that deficiencies in placentation may play a role, although positive evidence of placental pathology is not demonstrable in the majority of cases. Rarely the heart tones will suddenly stop entirely. When the baby is born in such cases we have been unable to find a satisfactory explanation after thorough post-mortem examination of the baby and gross and microscopic examination of the placenta. In some cases the placenta is long and narrow instead of the usual discoid shape, and on intrauterine palpation is found extending into both horns of the uterus. Abnormalities of the third stage of labor are not infrequent and retained placenta with manual removal is more often necessary than in normal cases. Post-partum hemorrhage has been slightly more frequent in our series.

Since 1926, we have had 7,553 deliveries at the Research and Educational Hospital, of which 155 were associated with this uterine anomaly. An analysis of the clinical course of the pregnancy and labor is interesting. It should be stated that all of our patients are charity teaching cases and all are delivered by interns and students. Only a small number of the more complicated cases are delivered by the resident. Cesarean sections and difficult forceps deliveries are done by the senior members of the staff. The patients for the most part were very carefully watched throughout labor, and interns and residents, as well as members of the attending staff check the diagnosis at various times during the pregnancy and labor. As was noted in our previous paper, the general impression received is that labor is rather long and tedious, and that many patients fail to go into labor at term. An indication that this impression is correct is afforded by the fact that it was necessary to induce labor in 25 of the 134 patients that delivered from below, or 18.6 per cent. In 8 of these it was necessary to use a Voorhees' bag after the failure of quinine and castor oil induction to furnish enough stimulus to start labor. As a corollary, it may be stated that 7 of the pregnancies definitely appeared to have progressed beyond the forty-first week. On the other hand, it will be seen that 18 out of 155 patients delivered at or before the thirty-sixth week, showing that prematurity as well as postmaturity is a complication to be expected. Twenty-one, or 13.5 per cent, of the patients were delivered by cesarean section, leaving 134 patients who were delivered vaginally.

These cesarean operations were for the most part indicated by the combination of a contracted pelvis and the arcuate uterus. The result of conservatism in the management has been so disappointing that we have become more radical in recent years. We particularly elected operative intervention in those cases in which premature rupture of the membranes complicated the problem of delivery, since a long drawn out labor frequently results in intrauterine infection which greatly increases the dangers of cesarean section if this operation becomes necessary. In one-fourth of the cases, the operation was indicated by the history of difficult labor in a previous pregnancy which was terminated by cesarean section. Premature detachment of the placenta was the indication for operation in 2 cases, and eclamptogenic toxemia in an equal number. One patient who had had a previous cesarean section had a rup-

ture of the uterine scar during the first stage of labor. We removed a dead baby from the abdomen and repaired the uterus, and the patient made an uneventful recovery. We plan to do a cesarean section at term in this patient if she becomes pregnant again.

Breech presentation occurred 15 times in the 134 patients who delivered from below, or 11.2 per cent. The incidence of breech in our clinic has been 3.5 per cent. The babies in this group showed an uncorrected mortality of 13.3 per cent, whereas our general mortality in breech is 7 per cent. Manual aid was practiced in all cases as soon as the umbilicus was born. In some cases the presence of a breech which could not be turned to a cephalic presentation by external version helped us to decide upon cesarean section together with other indications. The general mortality in breech is such that I believe that it is entirely unjustified to jeopardize these babies' lives when the outlook for safe delivery from below is seriously threatened by dry labor, prolapsed cord, and inefficient uterine contractions.

TABLE I

Hospital Deliveries	7,553
Bicornuate uteri	155—3.8%
Whites	121—2.6%
Colored	34—1.2%
Duration of pregnancy	
Less than 36 weeks	18
Over 41 weeks	7
Breech	15
Transverse	6
Oblique	5

TABLE II. DELIVERY

Labor induced	25
Watson	17
Bag	8
Cesarean section	21
Destructive operation	3
Forceps { Mid	3
{ Low	9
Post-partum hemorrhage	13
Placenta delayed	9
Manual removal	4
Average length of labor in primiparas	23.4 hr.

Transverse presentation which persisted during labor occurred 6 times and necessitated version and extraction once, embryotomy once, and cesarean section twice. The oblique type of transverse presentation rarely was persistent and as labor progressed the presenting part moved into the inlet and normal spontaneous delivery followed. There were 5 well-marked cases of this type.

Midforceps were necessary in only 3 cases and low forceps were applied 9 times. This tends to show that the greatest difficulty is in the first stage. Once the cervix is dilated and the head descends into the pelvis spontaneous delivery may be expected in the great majority of cases.

Postpartum hemorrhage in our clinic is any postpartum bleeding which equals or exceeds 500 c.c. Thirteen of the 134 cases had postpartum hemorrhage by this standard. This is double the number that occur in ordinary cases in the clinic.

Weak pains and long drawn out labors have been noted in my previous communication on this subject. The average length of labor in primiparas was 23.4 hours as compared with seventeen hours which is the time ordinarily considered normal for primiparas. Two of the cases extended 75 to 85 hours, respectively. On the other hand precipitate labors were seen quite frequently. Twenty-one out of 134 cases had labors lasting five hours or less and 7 of these labors occurred in primiparas.

Management.—The management may be summed up in the expression, watchful expectancy. As soon as the diagnosis is made in early pregnancy we begin to throw safeguards around the patient by explaining to her that abortion is somewhat more common than under normal circumstances. As a result, the earliest symptoms should be detected and appropriate treatment instituted at the first sign of threatened abortion. The patient is told to avoid undue fatigue, violent exercise and all physical strain, especially at the time of month she would be menstruating if she had not become pregnant. Those patients who present cramps or bleeding are promptly put to bed and given progestin, one rabbit unit twice a day until symptoms have subsided and twice a week thereafter until all evidence of abnormal uterine irritability has disappeared. If there has been a history of habitual abortion, the progestin injections are started twice a week prophylactically as soon as the diagnosis of pregnancy has been established.

As term is approached the possibility of premature labor is explained to the patient, and she is advised to enter the hospital as soon as pains start. If when this occurs the baby is nonviable or just on the border of viability, attempts are made to quiet uterine contractions by bed rest and progestin, and the patient tided over by these means until about the thirty-fourth week at which time the progestin is withdrawn and the patient allowed more activity.

Premature rupture of the membranes offers a problem for careful obstetric judgment. If the patient is a primipara not in labor and has a closed cervix, and a viable baby, we believe a cesarean section is indicated because of the uncertainty as to the onset of strong labor pains, the time of delivery and the possibility of intra-partum infection. If the patient is already in labor and rupture of the membranes is followed by strong pains a delay of a few hours is justifiable to determine what the character of the pains will be and how rapidly the cervix will dilate. If satisfactory progress is made in this period, labor is allowed to progress to spontaneous termination or forceps applied if necessary. If unsatisfactory progress is made, cesarean section is advised. With the rupture of the membranes the heart tones are carefully observed because of the danger of prolapsed cord which is potentially more common in this condition because of the frequency of breech and transverse presentation. If the heart tones are abnormally slow or rapid, careful rectal or vaginal examination is done to detect the presence of a prolapsed cord, and if found, appropriate treatment is instituted. Unless conditions are such that delivery can be rapidly and safely accomplished from below, we do a cesarean section.

As soon as labor is well established, we watch the heart tones carefully. If they appear to be dangerously rapid or very irregular, we terminate labor by cesarean section. If, on the contrary, the heart tones stay within normal range and labor seems to be progressing normally even if somewhat slowly, we adopt a conservative attitude and allow labor to progress to spontaneous termination if it will do so without the development of alarming symptoms on the part of the baby. Because of the uterine inertia so frequently observed the patient may have to

have rest periods during the course of the first stage and food and fluids must be supplied at regular intervals to prevent exhaustion and dehydration. For the same reason it is best to conduct these labors with as little sedation as possible, first because the pains are not so intolerable, and second because the stimulation to good uterine contractions should not be dulled by sedatives. In other cases the dilatation of the cervix must be carefully watched to prevent precipitate delivery. These cases are relatively rare in primiparas as compared with the prolonged labors.

The third stage is managed conservatively if bleeding is within normal limits. Pituitrin is given after the baby is born and manual removal is resorted to after two hours of ordinary third stage management. When the placenta extends into both horns, careful separation from the uterine wall must be practiced to prevent the retention of portions of placenta or membranes that might later give rise to postpartum bleeding. Following the birth of the placenta ergotrate is given by mouth or hypodermically to maintain good uterine contractions and thus limit blood loss.

The maternal mortality of 1.9 per cent indicates that the condition is to be regarded seriously as a complication of pregnancy and labor. All of these patients died following cesarean section after a prolonged test of labor, forty-one, thirty-six and fifty-two hours, respectively. Two of them had four-plus Wassermann reactions. All had contracted pelvis. One had an associated fibroid of the uterus and the membranes had been ruptured for fifteen hours. It would seem that we may have been too conservative in these cases and have allowed the test of labor to proceed too far before resorting to cesarean section. It is significant that 2 of the 3 occurred in our first 9 cases.

TABLE III. MORTALITY STATISTICS

Maternal	3	or	1.9%
Fetal	14	or	12.2% (uncorrected)
Stillborn	12		
Spontaneous delivery	5		
Abortions	2		
Macerated	2		
Destructive	3		
Born alive, died	2	or	1.4% (corrected)

Fourteen fetal deaths occurred in this series, an uncorrected mortality of 12.2 per cent. Twelve of these babies were stillborn; of these 3 died during labor, one was expelled into the abdomen and died following rupture of a previous cesarean scar, one was a 1,662 gm. syphilitic premature from a mother with eclamptogenic toxemia, the third was a 3,500 gm. baby for which no apparent cause of death could be found. Two other babies were born in poor condition and died. One was a breech, fifty-four hours in labor with extraction and forceps on the aftercoming head, and the other was delivered by low forceps after a fourteen hour labor, weighed 2750 gm., was in poor condition at birth and lived twenty-eight hours. The fetal mortality of the babies born alive was 1.4 per cent.

Of the 12 stillbirths, 2 were abortions, 2 were macerated, 5 occurred in spontaneous deliveries, 1 followed forceps extraction, 1 was a craniotomy, and 1 an embryotomy.

CONCLUSIONS

1. Pregnancy and labor in the arcuate type of bicornuate uterus is relatively of frequent occurrence.

2. While spontaneous delivery without serious complications usually occurs, there is a higher incidence of abnormalities in this group of patients than in women with normal uteri.

3. The complications of pregnancy are prematurity and postmaturity.

4. The complications of labor are prolonged first stage, breech and transverse presentation, sudden intrauterine fetal death, and retained placenta.

5. Cesarean section is more frequently indicated especially in cases when weak pains are associated with contracted pelves, or other major complications.

6. Retained placenta and post-partum hemorrhage are slightly more common.

7. Intrauterine fetal death early in labor should be anticipated by careful observation of the heart tones and prompt resort to cesarean section in appropriate cases.

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DISCUSSION

DR. WILLIAM C. DANFORTH.—This deviation from normal is caused by a failure of complete fusion of the Müllerian ducts at the level at which the fundus is formed. A less marked form of this abnormality is described by Kermauner which he calls uterus planifundalis. He refers to a muscular weakness which may exist in this latter form.

The signs by which the condition may be recognized have been well brought out. Emphasis upon the increased broadness of the top of the uterus in the second trimester and later is characteristic. It was easily demonstrable in a case I saw some time ago in which there was a saddle-shaped hollow between the uterine horns. In this case the horns were of approximately equal size, but one side of the uterus may be considerably larger than the other. Assuming the presence of a pelvis of normal size, and the absence of obstructing tumors, the presence of an oblique presentation in a primipara speaks strongly for this condition.

If uterus arcuatus could be observed in 3.8 per cent of a series of 7,553 cases, it is sufficiently frequent that some knowledge of the character of labor in its presence is important. It is interesting that the average length of labors in primiparas was 23.4 hours, a little longer than the average in normal women. The number of women who went into labor at thirty-six weeks or earlier is greater than would be the case in a similar number of normal gravidas. The normal incidence of breech of 3.5 per cent or thereabouts, is increased in this series of cases to 10 per cent. The transverse and oblique presentations are also greater than in a normal series.

When we look over the table of deliveries it is evident that abnormal labors are more frequent for we find 21 cesarean sections, 4 destructive operations, 13 postpartum hemorrhages, and 3 manual removals of the placenta. We may express our approval of the results so far as the fetus is concerned for a mortality of 1.4 per cent is excellent.

DR. RALPH A. REIS.—I was impressed with the first paper on this subject which Dr. Falls gave in 1924, in which he called this condition the ''saddle uterus.'' I am of the opinion that it occurs only in primiparas, for I have found it in a first pregnancy, but not in the second or subsequent ones. I wonder whether this is a structural or functional defect. I should like to know if Dr. Falls has any idea whether this condition may be due to a fundal implantation of the placenta. I would like to ask how many of these women were followed through subsequent deliveries and whether Dr. Falls found this in such pregnancies.

DR. FALLS (closing).—As to why this should be more common in white than in negro women, of course one cannot be too dogmatic. It might be related to the fact that colored women are better developed physically, have possibly more normal hormonal secretion, and their uteri develop more nearly normally in embryonic life.

The changes in menstruation in these 155 women might be another expression of their deviation from normal. Actually we expected to find a greater number of abnormalities of this type than we have.

With regard to Dr. Reis' question, we have not analyzed our cases in that connection. We have seen the deformity in multiparous women with irregular fetal heart tones. The shorter labors in multiparas reduce the number of observations of the fetal heart tones made in a given case.

INDIRECT EXTERNAL HYSTEROGRAPHY*

Con Fenning, M.D., Salt Lake City, Utah, M. Edward Davis, M.D., and Fred L. Adair, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital)

THE knowledge of the normal physiology and the pathologic variations of uterine motility is the key to many problems in clinical obstetrics. Studies of uterine activity have been diligently pursued on laboratory animals and the human being by many investigators. Although laboratory results have advanced our information concerning this subject considerably, such findings are not applicable in their entirety to the human being, for there exists much variation in the reproductive mechanism of laboratory animals and the human female.

Many different methods of experimental approach have been used. Some of these are suitable only for animal investigation. The methods of studying uterine activity in the human being are direct and indirect in character. A number of mechanical devices are available for use on the abdominal wall over the uterus. These procedures record the uterine action indirectly by eliciting the movements of the abdominal wall imparted to it by uterine muscle contractions. Dodek[1] has described such a tambour recording instrument and has used this successfully. External methods of hysterography have the advantage of simplicity and the ease with which they can be carried out in the human being. They need not interfere with the clinical conduct of the patient. Such indirect observations, however, provide only a gross picture of uterine activity. The minute changes which must necessarily precede gross action are lost in these indirect methods of

recording.   These changes may represent essential factors in under-
standing the mechanism of uterine motility.

Balloons have been placed in the uterine cavity and have been at-
tached to recording devices.   The displacement of their contents by
muscular contraction provides a means of measuring uterine activity.
The use of a rubber balloon introduces a foreign body within the
muscular organ which may lead to mechanical excitation of the
uterine myometrium.   In gross interpretations of uterine motility this
factor may not be important, but it may cloud more accurate observa-
tions.   Moir,[2] Adair and Davis,[3-5] and others have reported exten-
sively on this method of study, particularly during the early puer-
perium.   During pregnancy and labor these methods provide consider-
able technical difficulty which decreases their feasibility.   They have,
however, resulted in much progress and have provided an experi-
mental approach to the rational study of oxytocic drugs.

In vitro studies of human uterine muscle strips have been recently
reported by Adair and Haugen.[6]   These experiments do not simulate
true conditions in vivo, for they demonstrate only an isolated muscle
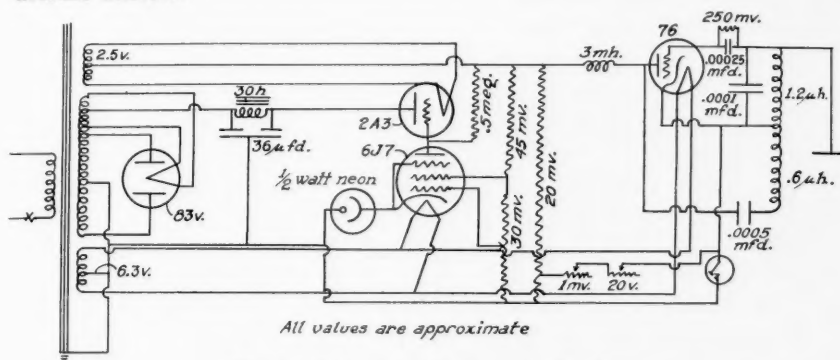response.   They have advanced our knowledge of the physiology of
uterine muscle.

Fig. 1.—Schematic diagram of circuit.

Adair, Davis, and Parsons[7] in 1930 carried out a series of studies on uterine
activity in women by means of an electrocardiograph.   These experiments recorded
action currents produced by uterine muscle contractions in a similar manner to the
recording of action currents by cardiac contractions.   Falk[8] in 1935 described a
similar method for use in nonpregnant individuals.   He developed a special
electrode that could be inserted into the uterine cavity, after which it was con-
nected with a sensitive string galvanometer.

The method described in this paper, although indirect in character,
combines the sensitivity of the electrical procedures and the ease of
application of the external recording devices.   By means of a specially
designed electrode and a sensitive string galvanometer, it measures
displacements of the uterus rather than action currents.   It need not
interfere with the clinical conduct of the patient so that recordings
can be made throughout pregnancy, labor, and the puerperium.
Graphs obtained by this method represent a true picture of uterine
motility.

The fundamental electrical circuit used here has been described elsewhere by Fenning.[9] Its use as an external hysterograph on rats and guinea pigs was first demonstrated by Bonar and Fenning.[10] The schematic diagram shown in Fig. 1 illustrates the modified circuit used at the present time.   Since the application to the human being is new, it was deemed advisable to prepare a preliminary report.   The purpose of this report is to point out the manner in which the recordings are
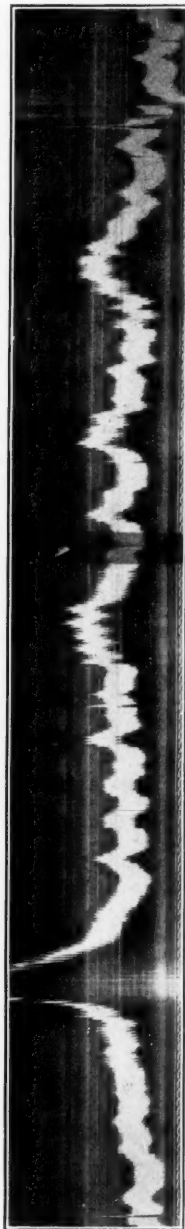

Fig. 2.—A typical complex curve showing the recording of the various components produced by maternal respiration, uterine motility, and fetal movements.

made, the qualitative analysis of simple and complex curves obtained by this method, and the presentation of typical recordings made during certain phases of pregnancy.

METHOD

Recording is accomplished by placing the fixed plate in proper relationship to the abdomen of the patient in the supine position. The plate is rigidly supported by a stand equipped with a micrometer control which allows the alignment and adjustment of the plate. The plate measures 5 by 11 cm. and is placed 2 to 6 cm. from the abdominal wall over the fundal region of the uterus. The exact distance depends upon the maximum anterior displacement during contractions. This is
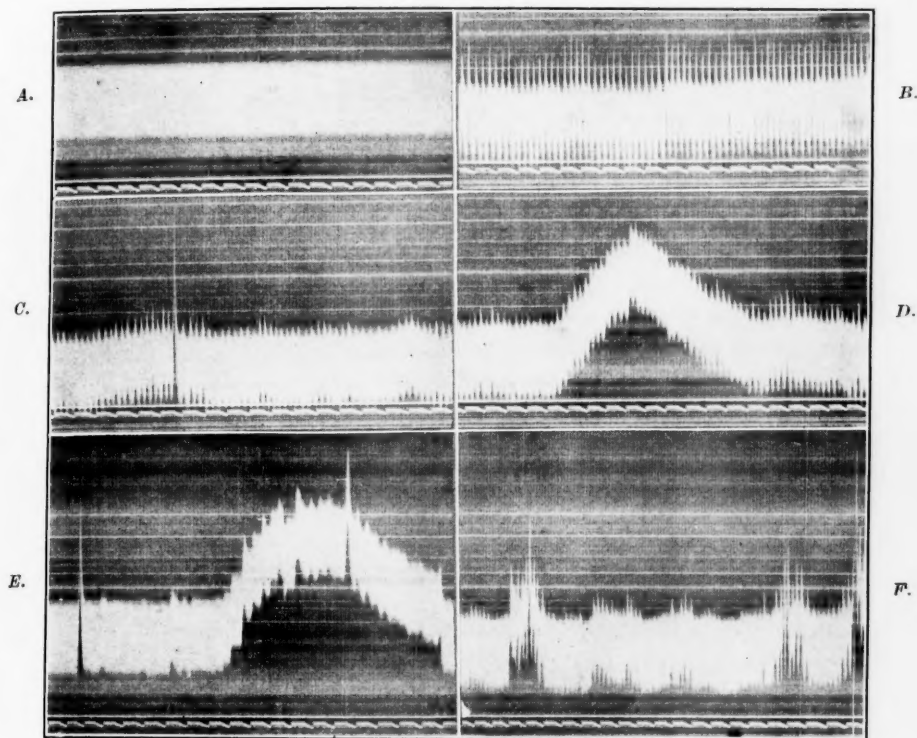
Fig. 2, *A*.—Blank test.

Fig. 2, *B*.—Maternal respiration. Mrs. H. (200637), aged 29 years, para 0, gravida i, 28 weeks' gestation, dead fetus.

Fig. 2, *C*.—Maternal respiration + sigh. Mrs. G. (198693), 39 weeks' gestation, live fetus.

Fig. 2, *D*.—Maternal respiration + uterine contraction. Mrs. H., aged 29 years, para 0, gravida i, 39 weeks' gestation, dead fetus.

Fig. 2, *E*.—Uterine activity, maternal respiration and sighs. Mrs. K. (188834), aged 23 years, para 0, gravida ii, post partum seven hours, packed uterus.

Fig. 2, *F*.—Maternal respiration, fetal activity. Mrs. W. (124570), aged 32 years, para ii, gravida iii, 39 weeks' gestation, live fetus.

determined by making preliminary observations to ascertain the extent of abdominal displacement to and from the plate. The plate distance is then adjusted to allow 0.5 cm. clearance over and above this movement. Usually a total distance of 2.5 cm. is satisfactory.

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THE QUALITATIVE ANALYSIS OF SIMPLE AND COMPLEX RECORDED CURVES

Any change in the position of the anterior surface of the abdominal wall with relation to the plate produces a deflection on the part of the movable member of the recorder. If the movement is toward the plate, the deflection will register in one direction on the graph, and if away from the plate, in the opposite direction. The extent of the deflection has a logarithmic relation to the actual displacement. Since the instrument has a fixed reactivity, it is possible to use the plate distance factor as a variable sensitivity control which acts to enhance or decrease the amplitude of deflection obtained with a given displacement. A greater distance of the plate from the abdominal wall allows for the recording of massive abdominal wall displacements, whereas a lesser distance permits the recording of minute abdominal wall displacements. It is apparent that the amplitude and the form of the displacement is recorded in a relatively nonlinear manner. The onset, duration, and the cessation of displacement can be ascertained in absolute time units.

Abdominal wall displacements may arise from a multitude of sources in either the pregnant or the nonpregnant woman. Each force which produces a displacement has its own characteristic form, amplitude, and duration. The forces may act singly, in sequence, or simultaneously. The actual displacement present at any one time represents the resultant of all forces acting to displace the abdominal wall toward or away from the plate electrode. The possible component factors which influence the response are:

I. Maternal origin:
1. Voluntary movements associated with the muscular and skeletal system.
2. Respiration and its modifications.
3. Uterine activity.
4. Gastrointestinal activity.
5. Transmitted arterial and venous pulsations.

II. Fetal origin:
1. Gross movements of the body and limbs of the fetus.
2. All other activities of the fetus capable of producing displacement of the abdominal wall, intrauterine fetal respiratory movements, fetal heart beat, and fetal hiccups, etc.

With a plate-abdominal wall separation capable of recording minute changes, any or all of the above components may produce a particular resultant curve. Such a curve is characterized by the fact that it is a pattern of many potentially possible curves. On the other hand, it is known that the various displacement components associated with the foregoing factors vary in amplitude. Hence, with an appropriate plate-abdominal wall separation, only the forces providing moderate

or strong displacements are of any consequence. Of the above, uterine activity, respiratory movements, and gross fetal movements ordinarily provide components. This is true only when complete cooperation is secured from the patient to eliminate voluntary movements of the body.
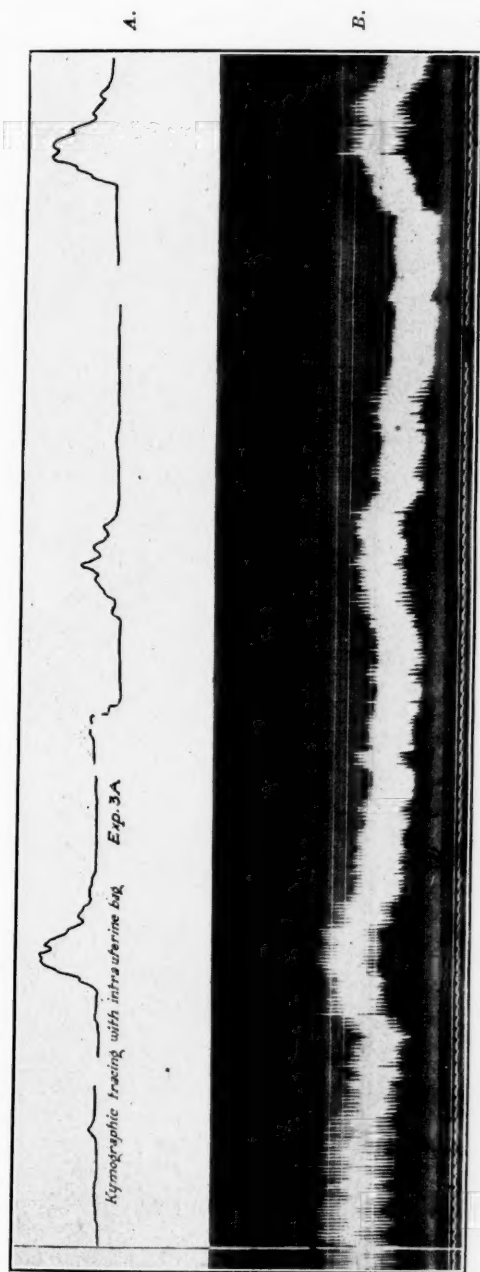
Fig. 3, A and B.—Simultaneous recordings of uterine activity on the sixth post-partum day. Mrs. S. A., para ii.

Fig. 2 represents a complex curve secured with a plate-abdominal wall spacing sufficient to allow for adequate recording of components produced by respiration, uterine activity, and fetal movements. The curve has certain definite characteristics which allow for relative analysis without the use of complex mathematical calculations. To clarify the complex curve, it was necessary to make specific recordings in which one or more typical recognizable components were present. In each case attention is called to similar appearing components present in the complex curve.
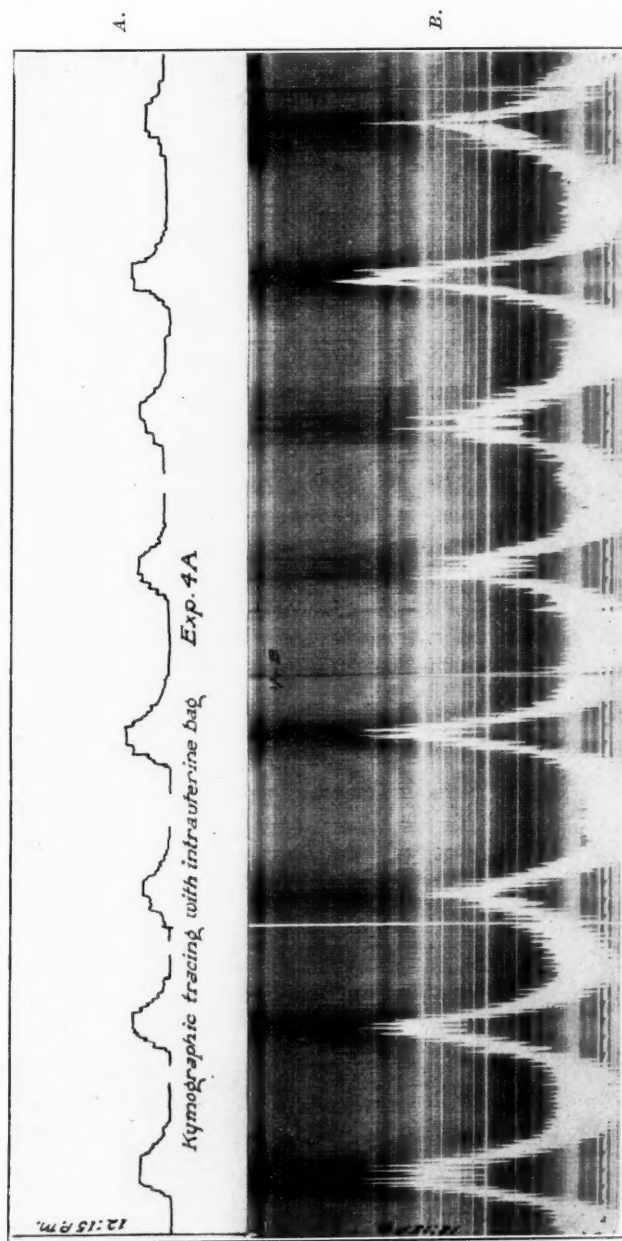
Fig. 4, A and B.—Simultaneous recording of uterine activity at the fortieth week of gestation.

Fig. 2, *A*. This curve shows a portion of a blank test. This shows the width of the stationary string shadow and the presence of a slow unidirectional drift amounting to 1 cm. per hour. The time recording device indicates ten-second intervals.

Fig. 2, *B*. This is a characteristic curve in which maternal respiration provides the principal deflection component. The upstroke is an indication of inspiration while the down stroke represents expiration. The curve provides indirect evidence of maternal respiratory activity. During inspiration the contraction of the diaphragm displaces the abdominal contents, which in turn displace the abdominal wall toward the plate. During expiration the recession of the abdominal wall to its approximate former resting position produces the reverse movement of the recording member. Respiration in this case is regular and has a frequency of twenty-one cycles per minute.
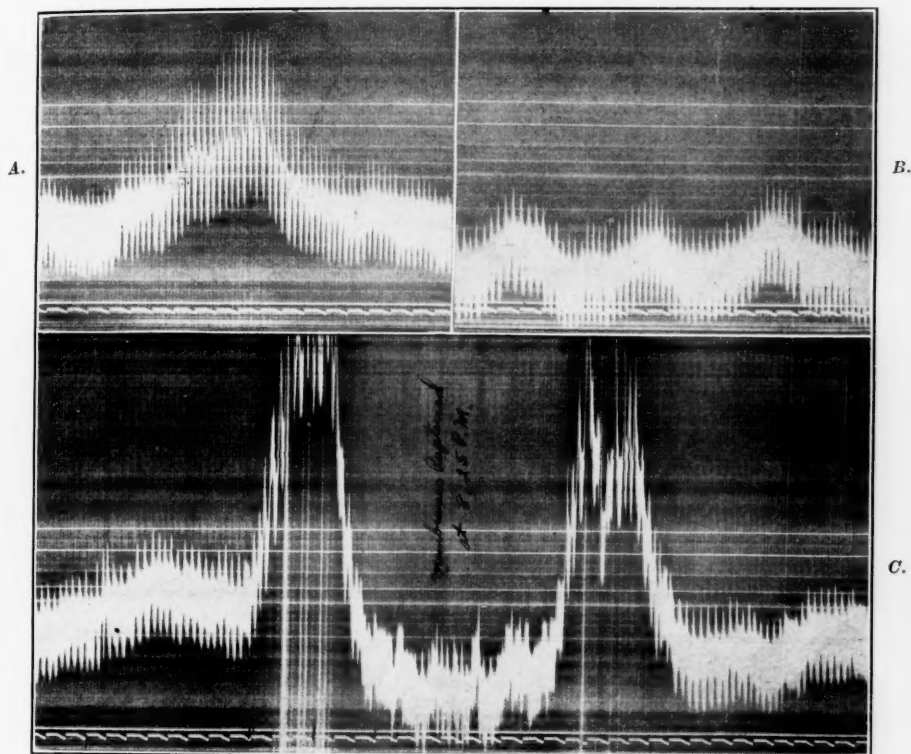
Fig. 5, *A*.—Painless uterine contraction (Braxton Hicks). Mrs. G. (198693), 39 weeks' gestation, five days before delivery.

Fig. 5, *B*.—Painless uterine contractions. Mrs. B., aged 23 years, para 0, gravida i, twenty-five days before delivery.

Fig. 5, *C*.—Painful uterine contractions and modified maternal respiration. Mrs. P. (188372), aged 18 years, para 0, gravida i, second stage of labor.

Fig. 2, *C*. The curve is somewhat similar to Fig. 2, *B* and differs only by the addition of a sigh or a natural deep inspiration.

Fig. 2, *D*. This curve illustrates the resultant displacement of the abdominal wall produced by maternal respiratory activity and a slower component resulting from painless uterine contraction. Attention is called to the fact that the respiratory movements show no change in frequency.

Fig. 2, *F*. This figure illustrates a typical graph in which the principal components are maternal respiration, sighs, and uterine contractions.

In order to provide positive proof that the slower component illustrated in Fig. 2, *D* is the result of the contracting uterus, simultaneous recordings with an intrauterine rubber balloon were made. These simultaneous recordings correlate the direct and the indirect approach.

Fig. 3. This figure shows the simultaneous recording of uterine activity on the sixth post-partum day. Curve in Fig. 3, *A* was obtained by means of an intrauterine bag and curve in Fig. 3, *B* was obtained by the method described in this paper.

Fig. 5, *D*.—A record of uterine contractions obtained early in the first stage of labor.
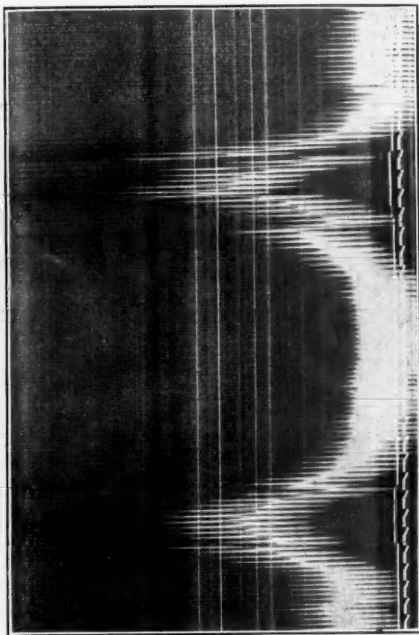
Fig. 5, *E*.—Painful uterine contractions, pain signalled. Mrs. G. First stage of labor.

Fig. 4.   These curves represent the simultaneous recordings of uterine activity at the fortieth week of gestation.   A small rubber balloon was introduced into the uterus for the induction of labor.   Four minims of pituitrin were given fifty minutes before the onset of the recording.   Fig. 4, *A* represents the graph of the direct approach while Fig. 4, *B* represents the graph obtained by the indirect method.

Typical Recordings of Normal Uterine Activity Ante Partum, During Parturition, and Post Partum.—Fig. 5, *A.*   This is a typical curve of uterine activity in the antepartum period, designated clinically as Braxton Hicks contractions.   Table I repre-

Fig. 5, *F.*—Uterine contractions in false labor.

Fig. 5, *G.*—A graph obtained three hours after expulsion of the placenta.

TABLE I. TEMPORAL ANALYSIS OF BRAXTON HICKS CONTRACTIONS

DURATION TOTAL	DURATION OF CONTRACTION	DURATION OF RELAXATION
130 seconds	25 seconds	105 seconds
110	45	65
170	55	115
160	85	75
110	55	55
110	55	55
120	60	60
180	55	125
165	80	85
130	70	60
140	75	65
80	30	50
90	45	45
150	55	95
90	30	60
180	50	130
75	35	35
100	45	55
220	180	40
100	40	60
140	90	50
120	60	60
145	40	105
115	45	70
95	50	45
95	50	45
160	40	120
128+ (Average)	60+ (Average)	68+ (Average)

sents the temporal analysis of 27 such curves obtained from patients observed from one to ninety days before labor.

Fig. 5, *B*. This illustrates another type of uterine activity frequently observed in the ante-partum period. Similar activity has been observed in the first stage of labor. The regular, rhythmic muscle action is generally of less amplitude and duration than the changes observed in Fig. 5, *A*.

Fig. 5, *C*. This graph was obtained from a patient during the second stage of labor. It is apparent that the respiration is modified by reflex and voluntary factors. The presence of the irregular rhythm, the slowing of the pulse rate, and the held inspirations are of significance. In addition to the modified respiration during the contraction, an alteration occurs between the contractions. This is due to conversation on the part of the patient concerning rupture of the membranes during the previous contraction.

Fig. 5, *D*. This is a record of uterine contractions very early in the onset of the first stage of labor. The patient signalled the onset, duration, and cessation of pain by means of a separate control. This record illustrates an apparent contraction threshold for pain, apparently related to the intensity of uterine contraction and intrauterine pressure. Contractions 2 and 3 were of subthreshold value and were not signalled by the patient as painful.

Fig. 5, *E*. This graph was secured from the same patient one hour and fifty minutes after Fig. 5, *D*. All contractions were accompanied by mild pain. During the first stage of labor, pain is not synchronous with the onset of the contraction. A latent period of approximately forty seconds is present between the onset of the contraction and the development of pain. The pain ceases approximately forty seconds before the termination of the contraction. Additional observations indicate that as labor progresses ordinarily the latent period decreases progressively and may occupy a period of less than one second.

Fig. 5, *F*. This graph was obtained from a patient in false labor. This graph is characteristic of this phenomenon. The contractions were accompanied by pain, thereby differing from the painless Braxton Hicks contractions of late pregnancy.

Fig. 5, *G*. This graph was made three hours after the expulsion of the placenta. During the expulsion the uterus underwent rhythmic contractions which had a frequency comparable to the second stage of labor. Thereafter the activity decreased progressively in frequency and in amplitude; at the same time the organ decreased in size. At the end of twelve hours, the uterus may show but one contraction per hour. In order to obtain normal recordings, it is essential that natural delivery of the fetus and placenta take place. Simple manual expression of the placenta is sufficient to alter the normal course of events.

SUMMARY AND CONCLUSIONS

A method is presented by which uterine displacements can be recorded. This method is highly sensitive, is not dependent upon mechanical contact and in no manner interferes with normal uterine activity or with the clinical conduct of the case.

Graphic recordings are presented of typical uterine motility previously known but inadequately recorded.

Potentially the method has considerable promise as a means of making studies previously found impossible.

The apparatus at present is not electrically or mechanically perfect.

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DISCUSSION

DR. A. C. IVY.—I have no doubt that very good mechanical records can be made of the movements of the uterus, if one is a good mechanic. Dr. Fenning has provided us with an electrical method, and I suspect if one is a good electrician he can get good records with the method. I am familiar with Dr. Fenning's device for pulse pressure, and I think it should be applicable for making records of the exact duration of the contractions of the uterus.

The records of pain are very much like the records of pain which occur with hunger contractions in the stomach. When the stomach contracts, the individual does not record pain until after the contraction is well on its way, as in uterine contractions. Usually the pain disappears before the contraction is completed. Occasionally the pain will continue after the relaxation period is completed.

I hope before Adair and Davis complete their work that they will make a record of the movements of the uterus from the abdomen, and simultaneously make a record with a balloon in the lower part of the uterus. The record from the abdomen should give us information of the time of onset of the contraction at the top of the uterus and the bag in the lower segment should give us the time of onset of the contraction there. The point I have in mind in making such

a double record is to find out whether or not the uterus manifests polarity, or whether the contraction starts at the fundus and proceeds toward the cervix, as it does in the dog and the monkey.

DR. M. EDWARD DAVIS.—The study of human uterine motility does not represent the simple process of recording the muscular action of the uterus. There are a number of factors which normally influence uterine motility. In the first place, there is the natural contractility of smooth muscle. Like all muscular organs the uterus undergoes periodic contractions which become grossly altered under changed conditions. Uterine activity is under hormonal control. Thus, in the nonpregnant individual, estrogenic and progestational hormones produce a varied uterine action which fits in with cyclical events. In pregnancy these hormones play an even more important role. Snyder was able to produce prolongation of gestation in the rabbit by the induction of a new set of corpora lutea in late pregnancy. Koff and Davis prolonged gestation by administering progestin to pregnant animals. These experimental procedures indicate how profoundly hormones control uterine action. Estrogenic substances probably increase uterine motility whereas the progestational hormone decreases uterine sensitivity. The normal reproductive process requires a proper balance of these two synergistic actions.

Metabolic factors must influence uterine action. Ivy and Danforth recently published experimental studies in which it was demonstrated that calcium plays an important role in uterine tone and motility. In the presence of an increased amount of available calcium, oxytocic drugs become more efficacious in their pharmacologic action, whereas they have little effect in the absence of sufficient calcium.

The uterus is under nervous control so that nervous stimuli should and do affect uterine action. The increasing interest in the endocrine control of the reproductive organs has relegated the nervous control to the background, but it cannot be totally ignored. Last, mechanical factors may influence uterine action. Muscle inherently reacts to physical stimuli of various types. In late pregnancy, minimal stimuli may provoke such a marked response that parturition is initiated.

It is important to regard labor as a phase of a long physiologic process which begins at the onset of pregnancy, reaches its climax with the onset of labor but continues on through the puerperium. The endocrines of pregnancy prepare the uterus for receptive stimuli at or near term. Just what initiates labor is still a matter for conjecture, but it can no longer be regarded as an isolated cataclysmic event unrelated to the entire process of parturition. To understand the nature of this important episode will require careful studies throughout the preparatory stage of pregnancy. Here we may obtain a clue as to what actually starts the process of labor and controls its character.

The method which we have presented in this paper offers an excellent approach to long-continued studies of uterine motility. The sensitivity of the method allows for the study of minute changes which precede or influence more gross changes. The method does not interfere with the normal conduct of pregnancy and labor, thereby making possible long-continued observations on the same patient. Such studies should throw light on the physiology of uterine activity.

DR. EDMUND JACOBSON.—Perhaps I can explain substantially how these records are secured, what their essential features are, and how the apparatus may be developed for physiologic purposes. The essential feature of the device is this plate. You are all familiar with the condenser, as used in a radio, which commonly consists of two plates set fairly close together. The intensity in each plate of the condenser, when other things are kept constant, always depends upon

the distance between the two plates. The second plate in this procedure is the abdominal wall itself, which, when it moves, alters the intensity in the plate shown in the figure. This alteration thereupon affects the rest of the circuit in such a way as to produce the recording with the galvanometer.

Therefore, by this device, uterine contractions are not recorded directly nor is anything recorded that goes on in the fetus. The record represents simply movements of the abdominal wall toward or away from the plate. These movements result partly from the uterine contractions, from the respirations and heartbeats of the mother, and from shifts of the fetus.

Obviously, these records are not to be confused with electrocardiograms, which show differences of potential in parts of the body accompanying the heartbeat; nor should it be confused with any method of recording the action potentials of uterine or other muscle. Clear recognition of these points will prevent errors of interpretation from a physiologic and gynecologic standpoint.

If desired, this apparatus could possibly be rendered more sensitive after a little experimentation. Instead of recording directly with the skin under the plate, if you place a second metallic plate on the abdomen, properly insulated but about the size of the one in the apparatus, and if you will furnish that plate with a little bias by means of C batteries, as used in radio, you can perhaps develop an apparatus which will prove much more sensitive.

DR. ADAIR (closing).—We are particularly anxious to find some method which will enable us to study uterine contractions without having to introduce any factor which in itself might modify them. This procedure does not introduce any foreign factor into the study as there is no contact with the patient.

I tried to make it clear that the recordings represent solely the reaction of the apparatus to the distance between the abdominal wall and the plate. Any factor that makes the abdominal wall move farther away or closer to the plate affects the curve. Consequently we will have to eliminate as far as possible anything that interferes with the movement of the patient, which will require complete cooperation on the part of the patient. We have also to establish a definite pattern of the different movements of the abdominal wall. I tried to show on the graphs how it was possible to pick out the respiratory movements and to differentiate the various types of movements of the abdominal wall from those produced by uterine contractions.

We are not trying to draw any very sweeping conclusions from our work. We simply offer this as a little study of a method which we think may have possibilities. Dr. Fenning is still working on the apparatus in an attempt to perfect it and determine if it has practical use.

Bonney, Victor: **Conservative Gynaecological Surgery,** South African M. J. **11:** 113, 1938.

Restoration to normal and preservation rather than destruction of pelvic organs in gynecologic operating is emphasized throughout the article. The psychologic and physical importance of such conservation is forcibly brought out. The abuses of hysterectomies, the performance of total hysterectomy where there is a clean cervix, and the removal of the uterus where a myomectomy would suffice are all criticized. Subtotal hysterectomy is recommended as the treatment of choice over irradiation in cases of severe menorrhagia in young women where curettage and endocrine therapy have failed, since it conserves ovarian function; however, utriculoplasty to reduce the amount of endometrial tissue and abdominal curettage are two measures which it is suggested be tried first.

Conservation of ovarian tissue to the extent of enucleation of innocent simple serous cysts and dermoids is advocated. Tubal conservation with later restoration to patency by insufflation or operation is advised whenever possible.

F. L. ADAIR AND T. G. GREADY.

PROLAPSE OF THE UTERUS, HYDRONEPHROSIS, HYPERTENSION*

A Probable Sequence of Events

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INTRODUCTION

IN A RECENT study[22] of 600 hypertensive vascular patients with regard to potential etiologic factors for the increase in blood pressure, 7 patients were discovered who had long-standing prolapse of the uterus with obstruction of the lower urinary tract. Although the incidence of procidentia was only 1.16 per cent, it seemed desirable to study further this type of gynecologic patient. In limiting this study to a specific type of obstructive lesion, we hoped to clarify the relationship between the urinary tract and hypertension.†

LITERATURE

An extensive review of the literature revealed no reports directly associating hypertension and prolapse of the uterus. In 1911, Hirokawa,[17] however, reported the autopsy findings of an eight-month-old infant with prolapse of the bladder, slight broadening of the ureters, and enlargement of the heart with normal valvular structures. Brettauer and Rubin[4] (1923) reported 11 cases of prolapse in which the blood pressures are recorded in 7. High blood pressure may be considered to be present in 4 of these. Hines and Piper[15] (1937) reported identical twins with prolapse and hypertension. They ascribed the hypertension to a hereditary factor as the mother was hypertensive. Unfortunately a genitourinary survey was not reported.

There are numerous studies which point out various types of urologic defects as a result of prolapse. Froriep[11] (1824) and Virchow[27] (1847) reported damaged urinary tracts resulting from prolapse. Halban and Tandler[14] in 1907 made a very extensive study of the anatomic relationship of the bladder and ureters involved in prolapse. They showed that the bladder was pulled down with the prolapsed uterus, frequently bringing the ureters with it. The herniation under such circumstances brought about pressure and bilateral dilatation of the ureters. Mirabeau[24] (1908) reported 3 cases of ureteral prolapse with hydronephrosis.

Later studies by Brakemann[3] (1928), Schmitz and Laibe[26] (1929), Frank[9] (1931, 1938), Graves, Kickham and Nathanson[13] (1936), Edwards[7] (1937), and Danforth[6] (1938) generously confirm the early reports of Halban and Tandler that prolapse of the uterus is associated frequently with dilatation of the ureters and hydronephrosis.

MATERIAL

The 15 cases comprising this study include patients encountered: in private cardiac practice, from the gynecologic service of Dr. Arthur

H. Curtis at the Passavant Memorial Hospital, from the service of Dr. George H. Gardner of the Northwestern University Medical School Gynecologic Clinic, from a female medical ward (64) of the Cook County Hospital.

Studies of these patients included a chronologic medical history, physical examination, and routine laboratory studies. Gynecologic examinations were made by Arthur H. Curtis and George H. Gardner. Urologic examinations were made by Donald K. Hibbs with cystoscopic examinations when possible as well as intravenous pyelograms, renal function, culture of the urine and blood studies for nitrogen retention. In the latter cases, we learned to utilize the compression effect of the prolapsed uterus for the intravenous pyelograms with better results than the conventional abdominal pressure. The cardiovascular studies included frequent blood pressure readings over as long a period of time as possible. Stethoscopic and percussion findings were uniformly supplemented with two meter roentgenograms and electrocardiograms. All of these patients had prolapse of the uterus present from one to twenty-one years (Table I). All of them had undergone two or more pregnancies. Other medical diagnoses are listed. The age range was from 37 to 75, averaging 55.8 years.

TABLE I. SHOWS THE AGE, DURATION OF PROLAPSE, BLOOD PRESSURE AND MEDICAL COMPLICATIONS OF 15 PATIENTS WITH VARYING DEGREES OF PROLAPSE

NO.	NAME	AGE YR.	BLOOD PRESSURE MM. OF HG	DURATION OF PROLAPSE YR.	MEDICAL COMPLICATIONS
1	L. W.	37	170/110	4	None
2	M. G.	37	140/100	14	Hypothyroidism
3	H. L.	38	180/120	1	Cholelithiasis
4	A. C.	46	232/122	10	Diabetes mellitus Arteriosclerosis
5	G. L.	48	150/100	2	Cholelithiasis Obesity
6	M. K.	52	210/120	2	Secondary anemia
7	H. K.	53	160/80	4	Arteriosclerosis
8	M. R.	55	170/90	4	None
9	C. K.	56	90/60	21	Uremia, shock Bladder stones Secondary anemia
10	M. C.	62	170/90	18	Cardiac insufficiency
11	E. M.	68	200/110	21	Diabetes mellitus Angina
12	E. H.	68	190/130	20	Myxedema Arteriosclerosis
13	M. M.	69	210/110	1	Syphilis Obesity
14	H. W.	74	190/110	15	Hemiplegia Arteriosclerosis
15	A. B.	75	200/100	20	Cholelithiasis Coronary sclerosis
Average		55.8	177/104	10.5	

The clinical details of these 15 patients are portrayed best by a description of 2 who are representative of the combination of prolapse and hypertension.

L. W. was a 37-year-old housewife. The past history revealed that she had had measles and several attacks of diphtheria, gonorrhea at 21, 9 pregnancies in two marriages. Four years before beginning attendance at the Northwestern University Clinic she noted protrusion of the uterus.

Subjectively, in 1938, she complained of frequency of urination, burning, urgency, nervousness, fatigue, backache, dyspnea, and the prolapse.
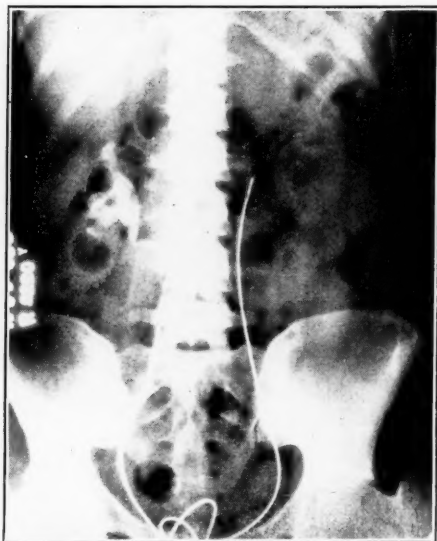

Fig. 1.

Fig. 2.

Fig. 1.—Case L. W. Showing apparently normal kidney pelves by intravenous urograms.

Fig. 2.—Case C. K. Showing marked bilateral hydronephrosis and dilated, tortuous ureters.

Objectively, she weighed 150 pounds and was 65 inches tall. The blood pressure readings ranged between 170/110 and 128/96. The heart measured 4.0 cm. to the right, 8.5 cm. to the left of the midsternal line and the transverse diameter of the chest measured 26.0 cm. The electrocardiogram showed a mild left axis deviation with borderline evidence of myocardial damage. Urologic studies (Dr. Donald K. Hibbs) disclosed a normal trigone, 1 ounce of residual urine, small ureterocele on the right, granular urethra, pus cells from both ureters and *Staphylococcus albus* from the right ureter with partial obstruction on the right. The kidney pelves were considered normal (Dr. E. E. Barth) (Fig. 1).

C. K., a 52-year-old widow, was admitted to the Passavant Memorial Hospital June, 1934. The family history revealed that her father died of a cerebral hemorrhage. The past history revealed that she had a full-term, forceps delivery in 1911, again in 1917, and during this latter pregnancy she noted a protrusion of the womb. For seventeen years, she was treated by conservative measures, until a few weeks before her entrance into the hospital when the prolapse suddenly became irreducible.

Subjectively, she complained of weakness, urinary frequency, incontinence, incomplete emptying of the bladder, constipation, and protrusion of the uterus which she was unable to reduce.

Objectively, the findings were only those of mild obesity, a soft systolic murmur at the apex, and massive prolapse with ulcerations and brawny edema. The prolapse was reduced under an anesthetic.

An intravenous pyelogram revealed a prolapse of the bladder and ureters with 25 or 30 calculi noted in the bladder. The ureters were dilated and tortuous, and the renal pelves showed bilateral hydronephrosis (Dr. James T. Case).

She re-entered the hospital four years later (1938) because of recurrence of the incarceration of the prolapsed uterus, which again had to be reduced under general anesthesia. She showed evidence of shock with a rapid feeble pulse and a low blood pressure ranging from 80/60 to 106/80. There was a high grade uremia; the blood urea nitrogen was 130.5 mg. per 100 c.c. of blood; the creatinine was 13.7 mg. per 100 c.c. of blood; the phthalein excretion was 20 to 30 per cent in two hours; the urine showed 4-plus albumin and usually was loaded with pus. The urine had a fixed specific gravity at 1.010. The blood counts showed a leucocytosis of 20,850 and no secondary anemia. This latter slowly developed over a three weeks' period. The blood nitrogen levels returned to normal in seven weeks.
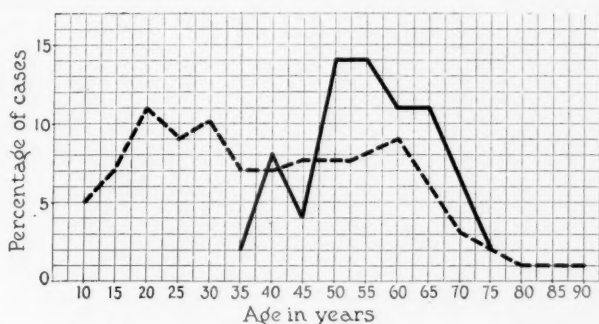

Fig. 3.—The broken line represents the percentage (ordinate) of female patients with hypertension (adapted from Riseman and Weiss). The solid line shows the percentage of hypertension in 84 patients with varying degrees of prolapse. The abscissa represents age periods in years.

This patient re-entered the hospital March, 1939 with a recurrence of the prolapse and mild uremia. The blood urea nitrogen was 33.1 mg. per 100 c.c. of blood and the creatinine was 2.78 mg. per 100 c.c. of blood. Cystoscopic examination (Dr. Donald K. Hibbs) showed gross trabeculation of the bladder. No indigocarmin dye was observed after thirty minutes. There was marked bilateral hydronephrosis and dilated, tortuous ureters (Fig. 2). The blood pressure ranged from 120/70 to 156/86. Roentgenographically, the heart measured 2.9 cm. to the right, 9.2 cm. to the left of the midsternal line, and the transverse diameter of the chest was 24.5 cm. (Dr. E. E. Barth). There was slight enlargement of the left ventricle. The electrocardiogram showed a left axis deviation.

The other 13 patients presented similar findings varying only as to detail. Gynecologically, in addition to prolapse, there were complications such as rectocele, cystocele, urethrocele and small fibroids.

Urologically, the patients presented variable roentgen findings by retrograde catheterization and intravenous urograms, from normal conditions to massive dilatation of the ureters and renal pelves. Urethral and bladder irritation were constant invariably with evidence of infection, usually *Bacillus coli* and staphylococci.

From the cardiovascular standpoint, hypertension was present consistently with varying levels in all patients (Table I) with the possible exception of the patient with the extreme uremia and shock due to the incarceration. Evidence of left ventricular enlargement was present from mild to extreme degrees as shown by the two meter roentgenograms. The electrocardiogram showed left axis deviation to be present in 10 patients and normal axis deviation in 5. Cardiac complications included congestive heart failure, coronary sclerosis and cerebral thrombosis.

An associated study of the incidence of hypertension in a somewhat larger series of patients with prolapse was made possible through the records of the

first 84 cases of prolapse entering the Passavant Memorial Hospital (courtesy of Dr. Arthur H. Curtis). Hypertension was found to be present in 61 of the 84 cases, or 73 per cent. The range of determinations of the hypertensive group was between 140/90 and 238/130. Actually, however, 97 patients were used in this study (excluding two duplications) and of these 74 had hypertension (76 per cent).

The age of these patients was from 36 to 76 years, and the duration of the prolapse from one year to twenty-seven years. Inasmuch as one would expect a high incidence of hypertension at these ages, it seemed desirable to compare our figures with a known standard. Riseman and Weiss[25] charted the frequency of hypertension in female patients entering the wards of the Boston City Hospital in five-year age groups. Utilizing this curve, we charted our series similarly, showing a definitely greater incidence (Fig. 3).

<center>DISCUSSION</center>

The recent reports of Longcope,[21] Butler,[5] Barker and Walters,[1] Leadbetter and Burkland,[20] Boyd and Lewis,[2] Leiter,[19] and Freeman and Hartley[10] show an increasing interest in the association of urologic disease and hypertension. The frequency of hypertension in our series of 97 patients with prolapse of the uterus and hypertension (76 per cent) would indicate strongly that the occurrence of increased blood pressure and prolapse cannot be explained solely upon a basis of coincidence. Factors commonly associated with increased blood pressure such as age, heredity and chronic nephritis were considered. Comparing our curve (Fig. 3) with that of Riseman and Weiss, to study the age element may seem presumptuous, considering the small number of our cases. At the ages of 50, 55, 65, and 70 years, however, our figures show almost twice as great a percentage of patients with hypertension. On this basis it would seem that the age factor could be excluded. With regard to the existence of chronic glomerulonephritis in these patients, the urinary findings were not characteristic of this disease, although transient albuminuria and casts were found in those patients observed over a period of years. The urologic evidence pointed to the infectious and obstructive character of the kidney lesion rather than to a true glomerulonephritis. It was impossible to obtain evidence which either proved or disproved the hereditary factor.

Specifically, we found the damage to the urinary tract to be varying degrees of hydronephrosis and hydroureters, with recurrent infection as has been reported by others. While the exact mechanism of ureteral compression does not seem to be entirely clear, obstruction is consistent with complete prolapse. Brettauer and Rubin[4] (1923) reviewed the various mechanisms of the production of urinary changes in cases of prolapse. They considered: (1) kinking of the urethra and stasis in a cystocele, (2) intramural stretching and stenosis of the ureters in the bladder wall, and (3) compression of the ureters over the edge of the levators forming the hernial ring of the genital prolapse. The uterine vessels may produce a constriction of the ureters (Fig. 4).

While obstruction of the ureters could be established readily with the prolapse complete, not all patients in our series could be proved as having a resultant hydronephrosis and hydroureters by present-day criteria. It had been thought that a direct relationship existed between the duration of the prolapse and the changes in the urinary tract. Statistics upon this point are fallacious, for in numerous instances previous treatment (pessaries, napkins, and surgery) had been used often with indifferent success, though often preventing complete prolapse. However, generally speaking, the patients having prolapse of short duration had minimal urologic changes demonstrable, while greater deformity was present where the procidentia existed for an extended period of time.
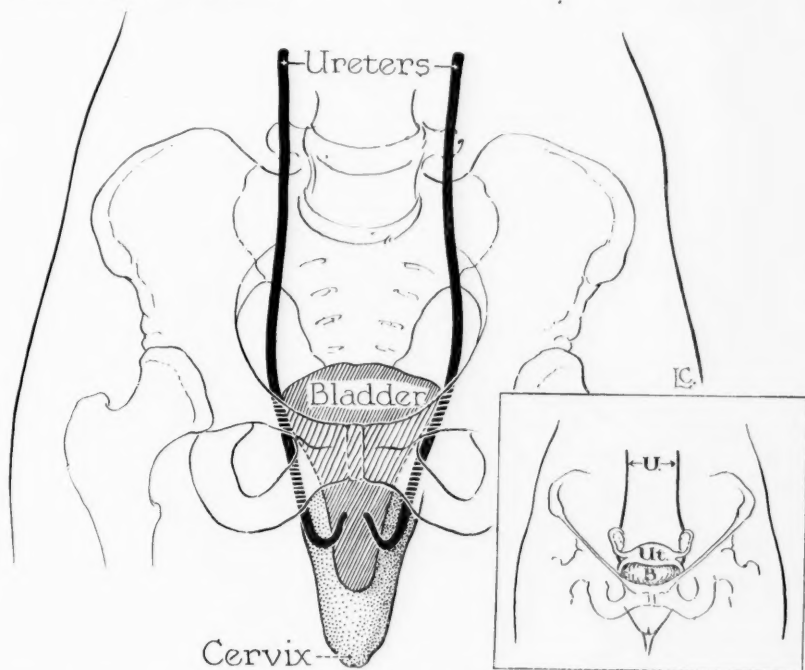
Fig. 4.—The diagram shows the schematic relationships of the ureters, uterus, bladder and bony pelvis in cases of complete prolapse. The insert shows the normal relationships.

Theoretically, it is possible for urinary obstruction, regardless of the cause, to produce hypertension. The role of obstruction in the production of hydronephrosis has been established. The significant studies of Kornitzer,[18] in 1922, proving a decrease in the blood supply of the kidney in hydronephrosis have not been appreciated sufficiently, and particularly so in light of the recent interest in experimental hypertension produced by obstructing the renal blood supply in animals (Goldblatt,[12] 1938). Similar studies include those of Hinman and Morrison[16] (1923, 1924) who produced hydronephrosis in rabbits, and, by using barium sulphate injections in the arterial tree, demonstrated a marked reduction in the main arterial and venous trunks of

the kidney cortex. In human kidneys with hydronephrosis, reduction of the blood supply was shown by the same technique. In 1938, Egger[8] repeated this work with similar conclusions. It is interesting that in no instances were blood pressure readings recorded in these works; whereas Williams, Wegria and Harrison[28] (1938) report an increase in the blood pressure of rats with spontaneous hydronephrosis.

The role of infection also must be considered as a factor. Clinically, all of these patients presented historical evidence that they had suffered from pyelonephritis and some were under observation with that diagnosis. Pyelonephritis is given as an intrinsic cause of hydronephrosis by Mathé[23] (1937).

In our previous studies we have pointed out that the diagnosis of essential or hypertension of unknown origin is not justifiable unless all defects of the urinary tract, acquired or congenital, are excluded. This study, although limited to a small series of patients with a relatively uncommon type of genitourinary pathology, appears to substantiate our original contention. It would seem that a perfect mechanism exists for the production of hypertension in patients with prolapse of the uterus, when the obstruction in the urinary tract produces hydronephrosis. The enlargement of the pelvis of the kidney encroaches upon the blood supply. The partial ischemia that results produces systemic hypertension by an unexplained mechanism.

SUMMARY

1. In 97 cases of prolapse of the uterus, hypertension was found to be present in 74, or 76 per cent.

2. It is suggested that prolapse of the uterus with resultant ureteral obstruction and hydronephrosis causes a decrease in the renal blood supply and hypertension.

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6 NORTH MICHIGAN AVENUE

DISCUSSION

DR. CHAUNCEY C. MAHER.—Our interest in this subject of hypertension and urologic pathology dates back over a number of years but this has been our first opportunity of studying a particular lesion where the obstructive mechanism was such an obvious one. Our former studies caused us to abandon the conventional viewpoint of dividing hypertension into the nephritic and nonnephritic or essential groups and led us to study the latter group with regard to mechanical defects of the urinary tract and the particular type under discussion this evening. We hoped to find some information as to the causative mechanism relating increase in blood pressure and obstruction of the urinary tract.

It would appear that in long-standing prolapse, hydronephrosis is a fairly consistent finding. Furthermore, it seems that hydronephrosis produces changes in the blood supply of the kidney. This has been shown by Goldblatt and others in animal experimentation to lead to persistent increase in blood pressure. The prolapse patients included in this study showed the usual findings of hypertensive vascular disease and the common complications. With the elevated blood pressure, there was enlargement of the left ventricle, sclerosis of the vascular tree, with congestive heart failure, coronary and cerebral thrombosis as complications.

The question should arise as to whether surgical treatment of the prolapse has produced a cure in the allied disease. To us this question is unanswered. We hope to follow as many of these patients as possible to learn whether or not the hydronephrosis is a reversible condition when the obstruction is relieved, and what effect, if any, this will have upon the blood pressure levels.

DR. W. C. DANFORTH.—I want to report a case which shows the effect of marked prolapse on the upper urinary tract. The patient was 84 years of age and had an enormous prolapse. The prolapse was reduced, and during her stay in the hospital we had some urinary studies made. On the left side we found hydroureter with hydronephrosis with two stones. On the right side was a similar hydroureter and hydronephrosis.

DR. EDWARD ALLEN.—I would like to ask if there was any study of the previous obstetric history in these patients. Hydroureter and changes in the kidney with hypertension are frequently the result of repeated pregnancies. Certainly these patients must have had repeated pregnancies to account for their prolapse.

DR. FRED L. ADAIR.—We must recognize that while the relation between prolapse and hydronephrosis and hydroureter is obvious, we cannot necessarily jump to the conclusion that hypertension is the farther result of this series of events. On the other hand, I do not see why hypertension should not result from a long-standing hydronephrosis which produces hypertension through kidney damage.

In comparing these various groups, there is a factor which should be taken into consideration. Practically all of these women who have a prolapse have obviously been previously pregnant and probably a number of times. We know that pregnancy predisposes to the development of hypertension or an aggrava-

tion of an existing hypertension. In the statistical analysis, the authors should take this into consideration, and consider parity in both the cases of prolapse and in their controls of the same ages.

DR. RALPH REIS.—This is the first attempt of which I am aware to correlate prolapse of the uterus with hydronephrosis and hypertension. Many of us who have seen many instances of prolapse of the uterus have not been aware of this relationship.

In 1928 we reported 202 patients with prolapse, many of these of long standing, and found a very low percentage of hypertension or cardiovascular disease. The second series of 220 patients ten years later showed the same thing. Hypertension occurred once in ten cases of prolapse. I am a bit fearful that if we accept the view expressed in tonight's paper too completely we will find creeping into the literature conceptions similar to the "myoma heart" of twenty or thirty years ago. These have taken many years to eradicate and are even today found in some textbooks.

I should like to ask the authors whether in relation to their study they took the opportunity of examining the eye grounds of these patients to rule out other pathology.

DR. J. D. MILLER.—I would like to ask the authors if they have studied the amount of residual urine in these patients and the relation of this to the production of hydronephrosis and other urinary tract pathology. Many of these patients are accustomed to sitting on the stool in such a way as to push the uterus up, bringing the urethra at the lower angle of the bladder so that there is less residual urine than one might expect.

DR. WOSIKA (in closing).—We hope to extend our studies to include the effect of pregnancy upon the urinary tract and hypertension. Most reports in the literature link pregnancy and hydronephrosis, and we hope to find a relation to cardiovascular disease.

That high blood pressure was found in only 10 per cent of Reis's cases seems a little startling. This is not higher than the average cases reported by Riseman and Weiss. One explanation might have been that we included only cases of complete prolapse.

Our patients showed typical eye ground findings where the hypertension was advanced. Unfortunately, we do not have complete data upon the amounts of the residual urine for the series.

We believe that the treatment of prolapse should be early and thorough to avoid the serious effects upon the urinary tract and subsequent general changes upon the cardiovascular system.

Bourne, W., and Pauly, A. J.: Thiobarbiturates in Obstetrics: Pentothal and Thioethamyl, Canad. M. A. J. **40:** 437, 1939.

The authors have studied two sulfur derivatives of barbituric acid, pentothal and thioethamyl, with regard to their analgesic and amnesic effects in obstetrics. The degree of analgesia was fairly good following pentothal and only moderately good after thioethamyl in a group of 100 patients. Amnesia was not nearly so marked as one would wish with either drug. It should be enhanced by the use of scopolamine at the time of the first or second dose of thiobarbiturate and not after. There was no excitement from pentothal and only slight in a few instances after thioethamyl. The duration of labor is shortened with the use of either compound. No harmful effects were noted in either mother or baby, with all infants breathing spontaneously. They believe that thioethamyl deserves further study particularly concerning optimum dosage.

CARL P. HUBER.

RELATIONSHIP OF HYDATID MOLE TO HABITUAL ABORTION

WITH A REPORT OF TWO CASES

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THE observation that chorionepithelioma is frequently associated with hydatidiform mole, spontaneous abortion, and in fact with any disturbance of the developing fetal trophoblast has stimulated extensive investigation of this pathologic condition about which so much still remains obscure. In the past four decades more than two thousand cases of chorionepithelioma have been reported, and it appears from these reports that the relative incidence of this most rapidly growing tumor is not as high as was formerly thought. The occurrence of this tumor following hydatid mole has been as high as 50 per cent with some observers, but the incidence in our own experience is more nearly 10 per cent, which corresponds with that of the two thousand reported cases. The fetal trophoblast no doubt develops hydatid changes more often than was previously thought and certainly many of the abortive types are not recognized. Every effort should be made, however, to determine their existence, because we know that repeated molar pregnancies may be the underlying cause for successive abortions, even if sometimes a normal pregnancy follows. Maternal mortality from mole itself may be as high as 10 per cent. The comparative ease with which the diagnosis of these pathologic changes can be made by acquainting oneself with the fairly typical clinical symptomatology, together with the use of the office procedure of aspiration biopsy, the Aschheim-Zondek and Friedman tests, should lead to more frequent recognition of these aberrant tendencies and to better judgment as to the proper care of them. Dependence on curettage alone is quite insufficient. The invasiveness of the lesion indicates that the pathologic changes may be in the myometrium. Possibly forthcoming substitutive hormonal preparations may offer a partial solution in therapy.

The following reports on two cases we have studied recently demonstrate successive abortive attempts at conception with tendencies toward hydatid changes or some other trophoblastic developmental defects. The unusual sequence of events in two individuals of the same age, similar physical development, parity and marital status is unique. The occurrence of a monstrosity and an accompanying acute hydramnios in one is the only essential difference in the clinical course of each patient. Hysterectomy was performed in both as a prophylactic measure, a procedure which we feel at the present time should be considered in other similar situations.

CASE HISTORIES

Case 1.—Mrs. T., a 24-year-old white woman, a nurse, had been married six years without any successful pregnancies. She was rather small of stature, underweight and of the general asthenic type. Her habits had been good and her menstrual history was $13 \times 30 \times 4$. Blood serologic tests for syphilis were negative. Her husband suffered from acute poliomyelitis at the age of 15 and at 30 has moderate residual weakness of the left lower extremity. Careful inquiry into the family history of the patient as well as into that of her husband fails to reveal any evidence of chronic disease, abortive tendencies, or fetal anomalies. The clinical course of this woman can be studied with better perspective if it be divided into five episodes which occurred over a period of five years.

Fig. 1.—Photomicrograph of hydropic villus from "blood mole" passed by Mrs. T., Oct. 25, 1935.

I. Following a period of two and one-half months of amenorrhea, a spontaneous abortion occurred in May, 1934. There was vaginal bleeding with the passage of dark clots of blood after which normal menstruation was restored. No laboratory studies were made to confirm the diagnosis of pregnancy and the cause of the abortion was not determined.

II. A few months later amenorrhea began the second time and on Sept. 19, 1935, the patient was first seen by one of us (F. E. O'C.). She appeared to be in her sixth month of gestation with a soft symmetrical uterus whose fundus extended to within 2 cm. of the umbilicus. No fetal movements nor heart sounds could be elicited and the patient, who was extremely pale and delicate, had felt no life. She complained of weakness and anorexia and had lost weight. A Friedman test was strongly positive. Operative delivery of the products of conception was considered but further observation was thought desirable. On October 22 a dark bloody vaginal discharge began and with this a few small clots were passed. The Friedman test was still positive. Two days later Mrs. T. was admitted to the Benedictine

Hospital and shortly thereafter expelled spontaneously a large homogeneous mass about 14 cm. in diameter. No part of a fetus was found in the mass nor could placental tissue be recognized grossly. The uterus was soft and boggy and there was moderate bleeding. Five hundred cubic centimeters of citrated blood was given intravenously, following which the patient reacted favorably and subsequently regained her health without significant untoward sequelae.

Nine weeks following the evacuation of the uterus a Friedman test was negative and after twelve weeks normal menstruation began. The patient had gained eight pounds, the uterus had returned to its normal size, and there was nothing suggestive of retained trophoblast in the uterus.

III. In July, 1936, Mrs. T. became pregnant for the third time. The diagnosis of pregnancy was established during the fourth month of gestation, and it proceeded normally until the eighth month when, over a period of three weeks, the abdomen became tremendously enlarged. The skin was taut over the symmetrically enlarged abdomen and signs of respiratory and circulatory embarrassment appeared. Roentgenograms showed a small fetus with an abnormal configuration of the head suggesting a malformation, a condition frequently seen with polyhydramnios. On April 1, 1937, the membranes were cautiously ruptured by making a small puncture through the fully taken up and slightly dilated cervix. The slow escape of amniotic fluid gradually brought about a decompression with only moderate maternal embarrassment. Shortly labor pains began and six hours later, under routine obstetric analgesia, a fetal monstrosity weighing three and one-half pounds was delivered. It was of a craniorachischisis type.

Subsequent aspiration biopsies of the endometrium were made at regular intervals and none revealed any pathologic changes.

IV. It was not until July, 1938, that the next pregnancy began. The Friedman test on July 25 gave a positive result. In view of the previous episodes this pregnancy caused much concern, and it was seriously questioned whether it could proceed to a successful termination with a resulting normal baby. Interference was not considered but the patient was carefully followed for evidence of abnormal trophoblastic development. During the sixth week of gestation spotting, bearing-down pains, and the usual signs of threatening abortion began. In spite of the daily administration of large doses of progestin (1 rat unit) and vitamin E (wheat germ oil m. lx) abortion occurred. The material expelled was not seen by us, but a thorough curettage was promptly done, and it yielded only endometrium showing pregnancy changes with huge tortuous glands in a stage of marked secretory activity and decidua. It would seem that the abortion was not the result of deficient corpus luteum activity. Once again a disturbance in trophoblastic development probably was the underlying cause. Six weeks later an aspiration biopsy of the endometrium yielded normal tissue and the Friedman test was negative. These findings allayed all fear that chorionepithelioma might be buried in the myometrium.

V. Mrs. T. and her husband were convinced that she was unable to carry through a pregnancy to a successful conclusion and requested some solution to the problem with which they were struggling. It was decided that complete hysterectomy with preservation of the adnexa was best adapted to her needs and this operation was performed Sept. 24, 1938. Recovery was uneventful and the patient was in good health six months later. The only pathologic change in the uterus was an extensive chronic endometritis.

CASE 2.—Mrs. S., a tall asthenic white woman, 29 years of age, had been married five years without becoming pregnant. Her health had always been good, blood serologic tests for syphilis were negative, and there was no history of her having been treated for this disease. Her husband was a normal healthy man 34 years old. No abortions had occurred during the pregnancies of the mother of either Mrs. S. or her husband.

The clinical course of this patient consisted of four distinct episodes spread over a period of five years.

I. Early in 1934 Mrs. S. became pregnant for the first time and at about the third month, spontaneous abortion occurred during which blood clots were said to

have been passed. No fetal elements were observed by the patient and no histologic studies were made. The menses when re-established followed a normal course until February, 1938, when the second pregnancy began.

II. It was on May 26, 1938, that Mrs. S. was referred by Dr. Eugene Galvin and at that time she was markedly dehydrated, had an albuminuria and was vomiting continuously. The fundus of the uterus was on a level with the umbilicus and seemed much larger than usual for a three months' pregnancy. The uterus was soft and boggy and the slight bleeding, which began two days previously, had become profuse. The Friedman test was positive.

Because of the patient's marked toxic state and the profuse hemorrhage, the uterus was evacuated with extreme caution. A huge quantity of material composed chiefly of grapelike masses was removed. Grossly and microscopically this was a hydatidiform mole without evidence of chorionepithelioma.

The uterus contracted promptly, no enlargement of the ovaries could be felt, and following a blood transfusion recovery was prompt. An aspiration endometrial biopsy on July 11, 1938, revealed some retained decidual tissue invading the myometrium, but the Friedman test was negative. These procedures were repeated early in September following two normal menstrual periods, and it was found that the endometrium had returned to the normal proliferative state and the Friedman test was still negative.

III. On Nov. 22, 1938, Mrs. S. was seen again at which time she gave a history of having missed two periods. A day or two before, she began to flow and to pass clots. She appeared ill. The uterus was enlarged to the size of a three months' gestation. The cervix was soft and patulous and through its canal blood was emitted. After the collection of urine on the following morning for a Friedman test, later reported positive, a curettage was performed. A practically homogeneous mass of blood clot with some placental debris in which no fetal parts were discernible was removed. Some of the villi showed hydatid alteration while others were fibrotic. Intermittent bleeding persisted for two weeks. Nausea and a feeling of exhaustion continued and the pregnancy test was still positive. The uterus was sufficiently well involuted so that thorough curettage could be done. The scrapings contained bits of myometrium invaded by Langhans' cells and scattered syncytial cell masses. These findings were suggestive of chorionepithelioma, but a definite diagnosis of this tumor could not be made. Three weeks later the pregnancy test was negative.

IV. Here again as with Case 1 it seemed that a successful pregnancy was highly improbable, and it was decided that a complete hysterectomy with preservation of the tubes and ovaries was the correct solution of this woman's problem. This operation was performed on Dec. 29, 1938. An apparently receding corpus luteum was seen on one ovary. No evidence of hydatidiform mole or chorionepithelioma could be found. A fairly large adenomyomatous infiltration was present in the wall of the uterus.

SUMMARY

Two very similar cases of habitual abortion are presented. The first pregnancy in each instance ended in simple abortion, the underlying pathologic changes of which were not determined. Each subsequent pregnancy resulted in either aberrant trophoblastic development or fetal anomaly. Complete hysterectomy with preservation of the adnexa was performed for prophylactic reasons on both women.

COMMENT

Successive molar pregnancies or those resulting repeatedly in aberrant trophoblastic development are supposedly uncommon, although Osborn in 1863 reported "uterine hydatids in four successive gestations." Lemaire observed as many as 6 in the same individual. These observations were not substantiated by histologic studies. Findley reported 31.4 per

cent incidence of chorionepithelioma in his series of 500 cases of mole. On the other hand O. A. Gordon found only 21 moles out of 4,500 abortions. De Lee reported 16 cases of mole, none of which developed chorionepithelioma. We believe that careful pathologic studies will reveal a greater incidence of these occurrences than the literature indicates. Storch has already called attention to the fact that the large grossly vesicular mole is an unusual finding in molar pregnancies. With this statement we thoroughly agree. It is well known, of course, that a normal pregnancy can follow hydatidiform mole and fetal anomalies. Certainly hysterectomy should not be done because of such isolated instances; however, we feel quite strongly that this is the procedure of choice when four or more pregnancies are terminated by these pathologic processes. Not only is the risk of the development of chorionepithelioma eliminated but repeated episodes which jeopardize the physical well-being and even life of the patient are brought to an end.

If Ewing's suggestion that these pathologic processes are the result of abnormal ovarian activity is found to be true, then the time may not be far away when these tendencies can be controlled by hormonal preparations and the radical procedure herein recommended will be unnecessary.

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Baker, Ranson, and Tynen: A New Chemical Contraceptive, Lancet 2: 882, 1938.

The authors report progress in the search for an efficient chemical contraceptive. Phenyl mercuric acetate has been studied both experimentally and clinically with good results. It has a spermicidal action in $\frac{1}{1025}$ per cent concentration in an acid and $\frac{1}{256}$ per cent concentration in an alkaline medium. They believe it to be harmless and nonirritant as established by both experimental and clinical tests. Prepared in a gelatin base it has proved to have a greater spermicidal effect than any substance on the market and is rapidly diffused. They have also prepared it in paste form for use with the occlusive diaphragm.

In preliminary clinical tests it has proved satisfactory in their opinion. The data which are presented in this regard are inconclusive, as only 11 women using this substance only for periods of 1 to 12 months are reported. One pregnancy is reported.

CARL P. HUBER.

GRANULOSA CELL NEOPLASM WITH A DISCUSSION OF POSSIBLE HISTOGENESIS*

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THE histogenesis of granulosa cell neoplasm has been in dispute ever since Rokitansky, in 1855, provided the first example. A follicular pattern, with Call-Exner bodies, was early noted and the various designations given this tumor, such as "folliculoma," "folliculoma malignum," "adenoma of the Graafian follicles," and so on, are evidence that an origin from mature granulosa cells was considered probable. In the second decade of the twentieth century, however, the pendulum swung to a concept of derivation from granulosa cell rests. Meyer,[1] the chief exponent of this "rest hypothesis" based his conclusions on the following observations: (1) The proliferative activity, and probably the existence of the granulosa cell in the follicle, are dependent on the integrity of the contained ovum. (2) The number of follicles is not increased after birth. (3) Follicles suffer atresia at the time of menopause, while the peak of incidence of granulosa cell tumor occurs at a later period. (4) Granulosa cell rests are often found in the hilar regions of the ovaries of patients of all ages. Meyer's conclusions were strengthened by Te Linde,[2] who found a very small granulosa cell tumor in the ovarian hilus of a patient aged fifty-three years.

Interest in the "follicular hypothesis" was once more aroused by Robinson,[3] in 1923. This author, reporting his cases of granulosa cell tumor, observed in one definite evidence of follicular hyperplasia in the nontumorous remnant of the ovary. Recently Butterworth[4] made a definite contribution to the subject. Repeating some earlier work by Brambell, Parkes and Fielding,[5] on the effect of roentgen rays on the ovaries of mature female mice, he was able, in a number of instances, to produce tumors histologically and "functionally" identical with granulosa cell neoplasms. The primary effect of the rays was, he found, complete destruction of all ovocytes and degeneration of the follicles. In the cases in which there was evidence of development of granulosa cell neoplasm, direct origin of the tumor from residual follicular epithelium was established. Luteinization of some of these elements also was observed in a few cases, with the development of true luteomas. Butterworth's work, while not entirely nullifying the "cell-rest hypothesis" of histogenesis, lends, it would seem, considerable weight to the argument that degenerating Graafian follicles can give rise to tumors.

In a previous review[6] of some 400 solid ovarian tumors removed surgically at the Mayo Clinic, 30 examples of granulosa cell neoplasm were described. In none of these cases was it possible to draw conclusions relative to histogenesis. Recently in a study of papillary

ovarian cysts,[7] one additional example of granulosa cell neoplasm was brought to light. It is with full realization of the dangers of trying to establish histogenetic data from a study of fully developed neoplastic processes that we are reporting this case. The occurrence of a coexisting adenocarcinoma furnishes an additional feature of interest.

<div align="center">REPORT OF A CASE</div>

A married, white primipara, aged 53 years, was admitted to the clinic Aug. 18, 1920, because of postmenopausal bleeding. Her family history and personal history were negative. Menses had been regular and the menopause, which had occurred at the age of 47 years, was without incident. A year and a half prior to admission she had begun to have frequent vaginal spotting which had increased in severity to a profuse flow, lasting from three to ten days. These episodes of menstruallike bleeding had continued, with more or less cyclic regularity, until the time of admission. In addition to this symptom the patient gave a vague history of biliary dyspepsia, two years in duration. Urinary frequency had been present for six months. The positive physical findings were a large uterus and a mass in the cul-de-sac. Laboratory data gave essentially negative results.

Aug. 28, 1920, total hysterectomy was performed with removal of both adnexa, for a cystic tumor of the right ovary. Adhesions or metastasis were not noted at the time of operation. Sept. 9, 1920, cholecystectomy was performed for chronic cholecystitis. The pancreas appeared enlarged and the duodenum was adherent to the under surface of the liver.

The patient's condition remained satisfactory for a time but on Oct. 12, 1920, pleural effusion developed on the right side. This was aspirated Oct. 19, 1920, and 1,500 c.c. of slightly turbid fluid obtained. Drainage by catheter subsequently became necessary because of reaccumulation of fluid, but in spite of this the patient's condition remained fairly satisfactory. In November, 1920, however, subcutaneous nodules appeared at various situations over the patient's body. Dec. 20, 1920, one of these nodules, situated on the scalp, was taken for biopsy. A diagnosis of metastatic adenocarcinoma was made. Progress from this time was rapidly unfavorable and symptoms and signs of chronic intestinal obstruction developed. Death occurred Jan. 4, 1922.

The surgical material of interest in this case consisted of the uterus, both tubes, and both ovaries removed Aug. 28, 1920, and the material removed from the scalp for biopsy on Dec. 20, 1920.

Pathologic Features.—The uterus was about twice normal size and measured 6 by 4 by 4 cm. Both oviducts gave evidence of chronic inflammatory thickening. The left ovary was atrophic. The right ovary was entirely replaced by a cystic-solid tumor measuring 10 cm. in diameter. This tumor had a smooth, glistening grayish brown surface. On section, the tumor appeared honeycombed with cysts measuring up to 2 cm. in diameter and filled with a coagulated material. Between the cysts the substance of the tumor was brown, soft and of a homogeneously granular appearance. Fibrous tissue was small in amount (Fig. 1).

Microscopically, the endometrium was thickened and presented the picture of cystic, glandular hyperplasia so commonly associated with granulosa cell neoplasm. The left ovary and the right and left oviducts were not remarkable. The tumor of the right ovary presented the cardinal microscopic features of granulosa cell neoplasm, with a preponderance of folliculoid and cylindroid patterns. The following atypical features, however, were noted: (1) the presence of large cysts, filled with material suggesting liquor folliculi, and lined by many layers of tumor cells, but with absence of ova; (2) in certain places, notably near the periphery of the tumor, the appearance of normal follicular remnants, again without ova, presenting evidence of proliferative activity of the granulosa cells, often confined to one portion of the follicle (Figs. 2, 3, and 4).

Sections of the nodule removed from the scalp revealed the picture of adeno-carcinoma, Grade 2. The cells lining the alveoli were tall, columnar and had basal nuclei showing mitotic figures. Stains for mucus were positive. In no instance was there any resemblance to the picture presented by the ovarian tumor. Sections of the gall bladder disclosed the presence of typical chronic catarrhal cholecystitis.

Fig. 1.—The smooth surface of the tumor and hypertrophy of the uterus are evident.
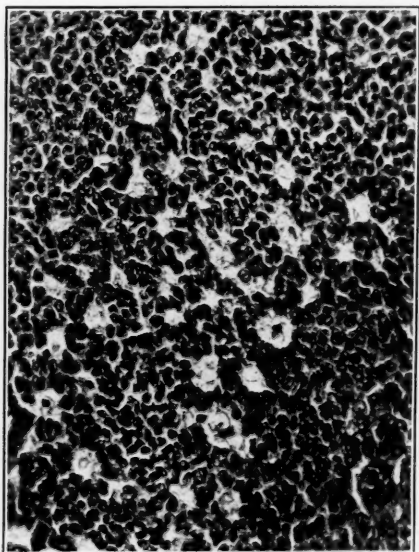
Fig. 2.   Fig. 3.

Fig. 2.—Typical granulosa cell neoplasm. Folliculoid pattern with Call-Exner bodies ($\times 275$).
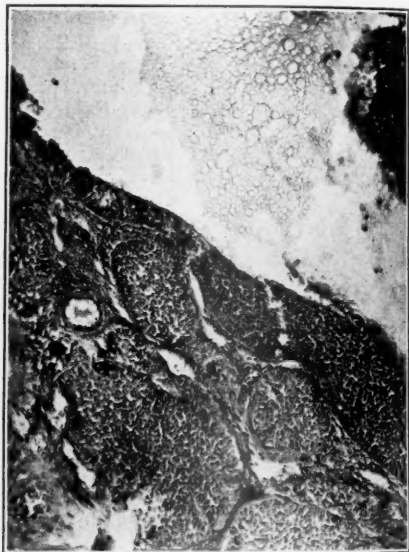
Fig. 3.—Cylindroid structure and large, cystic follicle ($\times 80$).

Permission was obtained to perform post-mortem examination of only the thorax and abdomen and the stipulation was added that tissue of the various organs saved for study be limited to sections for microscopic examination. This circumstance made complete investigation impossible. The following data, however, were noted on gross inspection: There were multiple, discrete, subcu-

taneous nodules measuring up to 3 cm. in diameter and situated on the scalp, dorsum of both hands, anterior aspects of the thorax and abdomen, gluteal regions and lower extremities.   Nodules in the intestinal wall had caused partial obstruction of the terminal portion of the ileum, also there were nodules on that part of the peritoneum which covered the urinary bladder, in the periaortic

Fig. 4.—Portions of two hyperplastic follicles and adjacent portion of tumor (×85).

Fig. 5.

Fig. 6.

Fig. 5.—Adenocarcinoma, Grade 2, of pancreas (×100).
Fig. 6.—Metastatic adenocarcinoma of skin (×250).

lymph nodes and in the adrenal glands.   A rather large nodule was present in the body of the pancreas, and there were other nodules in the liver.   Scattered nodules were found in the lungs, on both pleurae, on the pericardium, in the myocardium, and in the mediastinal lymph nodes.

Microscopic examination of nodules from all of these various tissues revealed the same picture; namely, adenocarcinoma, Grade 2, in which there was a

tendency toward formation of ducts and alveoli. The carcinoma cells were of a tall, columnar type, with basal nuclei showing a moderate number of mitotic figures. A small amount of mucus was demonstrated in the tubular and alveolar spaces. Invasion of lymphatic channels by groups of malignant cells was evident in many of the sections and invasion of the adrenal vein was observed. None of the microscopic sections bore even the slightest resemblance to the picture presented by the ovarian tumor (Figs. 5 and 6).

<center>COMMENT</center>

The history, physical findings, and gross and microscopic characteristics in this case of ovarian tumor were all typical of granulosa cell neoplasm. However, the presence in these neoplasms of cysts resembling overgrown follicles is a rather unusual finding. Although it is difficult to deduce histogenic data from sections of any large tumor, it would seem, in this instance as in Robinson's case, that an origin from follicular epithelium is probable. Many follicles, appearing otherwise normal, presented localized hyperplasia of the granulosa cells with extension to involve the surrounding tissue. The absence of ova falls in line with the observations of Butterworth on the experimental production of granulosa cell tumors in mice.

In regard to the course of the disease in this case, subsequent to operation, one conclusion only seems justifiable: The metastatic nodules were not ovarian in origin. Sections taken from many parts of the ovarian tumor all presented the picture of granulosa cell neoplasm. In contrast, sections from skin, adrenal glands, lungs, heart, pancreas, and other tissues were uniformly characteristic of adenocarcinoma. To this extent only did the partial necropsy clarify the sequence of events. In retrospect, however, there come to mind the complaint of vague upper abdominal discomfort, cholelithiasis for which cholecystectomy subsequently was performed and the surgical note regarding the adhesions around the pancreas, duodenum and liver. It is known that sometimes there are few early manifestations of pancreatic carcinoma. It is known, also, that a growth in the pancreas may give rise to metastatic nodules which often overshadow the primary growth. The alveolar and tubular arrangement seen in sections of the various metastatic nodules in the case under consideration are often reproduced in metastatic carcinoma arising in the pancreas, but further than this we cannot go.

<center>SUMMARY</center>

In an unusual case of granulosa cell neoplasm, there was evidence to support the view that this tumor arises from follicular epithelium. The patient died five months after operation from carcinoma which was extraovarian in origin.

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IMMEDIATE PERINEORRHAPHY WITH KNOTLESS SUTURES*

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IN JANUARY, 1937, I reviewed the history of perineorrhaphy and reported 449 repairs in which knotless sutures of chromic catgut were used.[1] There was one failure in this group, the lower half of one wound breaking down on the third or fourth day. A second repair with sutures of silkworm gut was done on the sixth day and this resulted in a primary union. I now wish to report upon my experience since that date.
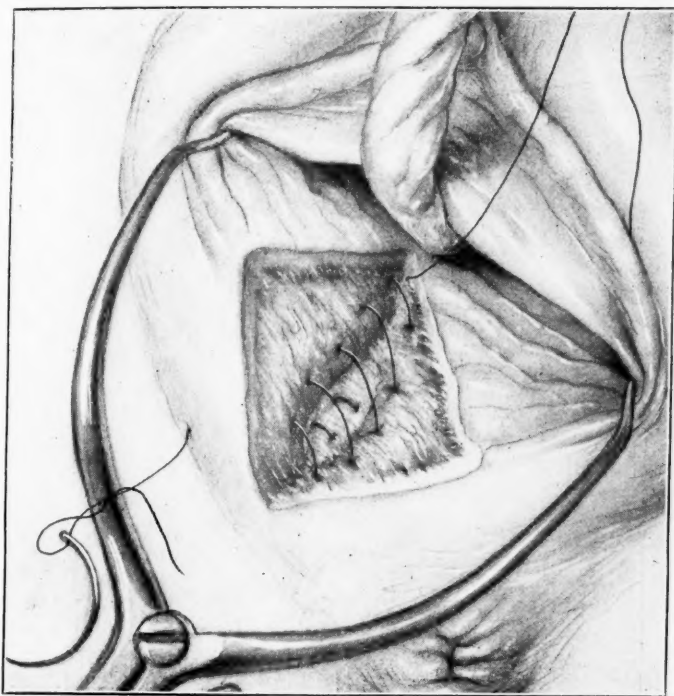

Fig. 1.—First layer, continuous suture. No. 1 chromic catgut.

There have been two minor changes in my technique. When there is free bleeding from the episiotomy wound, I use a continuous whipstitch for the deepest suture instead of the continuous mattress suture. This can be put in more quickly and controls the venous bleeding better. The second change consists of through-and-through sutures when a tear extends up the vaginal sulcus beyond the point where submucous sutures can be conveniently placed. The first suture secures both edges of the laceration as high up in the vagina as it is possible to place it. It then serves as a retraction suture and other sutures are placed one above the other until the upper angle of the wound is reached. The operation is then continued as I described in my first paper. The first row of sutures, proceeding from side to side of the wound, closes the deeper layers. When it finally reaches the lower end of the wound, it is brought out through the skin as far away from the anus as possible.

*Read at the Greenbrier Interstate Medical and Surgical Society, April 17, 1939.
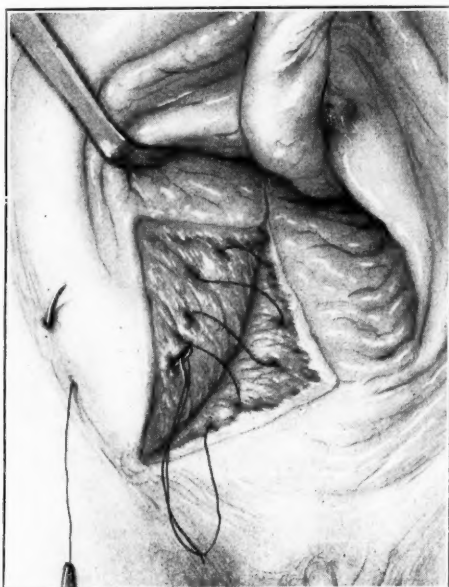
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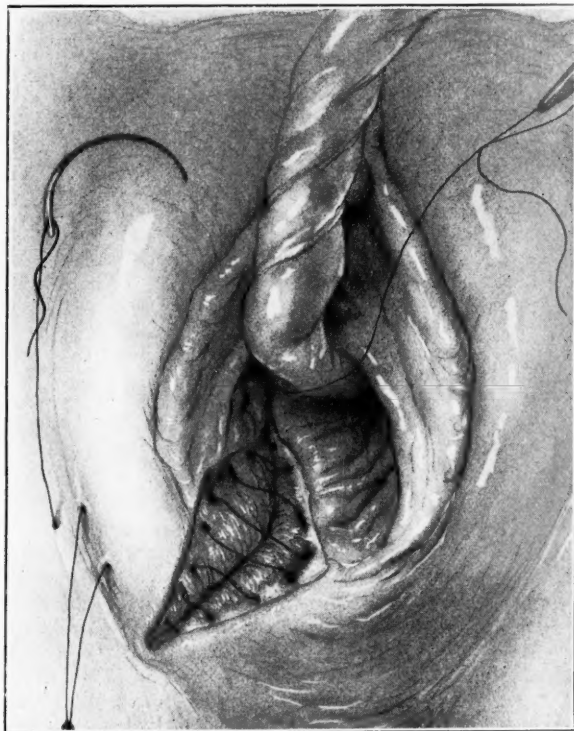Fig. 2.—Second layer, continuous mattress suture. No. 1 chromic catgut.

Fig. 3.—Third layer, continuous mattress suture. No. 1 chromic catgut.

I might say that the needle I use is a round curved needle with a radius of one-half an inch. This permits bringing the suture through the skin some two inches or more from the anus. A clamp is put on the suture and dropped. The weight of the clamp keeps the end of the suture out of the way. The other end of the catgut strand is then threaded on the needle and the second layer of sutures placed in a similar manner. This still further narrows the troughlike wound. This suture is brought out through the skin in the neighborhood of the first suture. The third layer of sutures is placed with one-half of a new strand of catgut. Care should be taken with this suture to bring the surface markings, such as the hymenal ring, the mucocutaneous junction, and the pigmented skin, opposite one another. The remainder of the second strand of catgut serves for the fourth layer which is a submucous, subcutaneous suture.
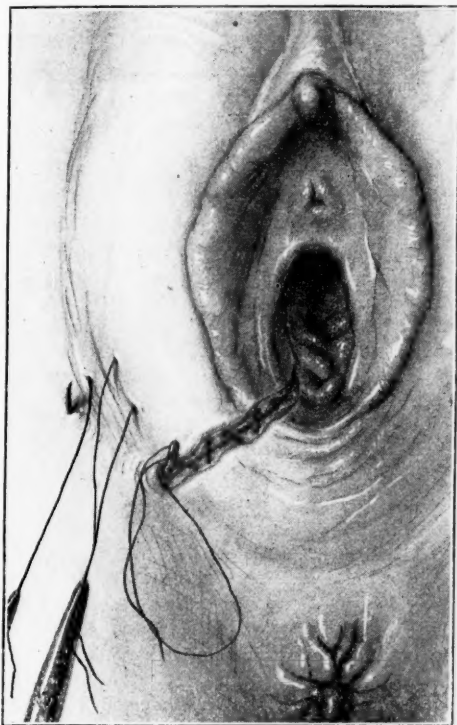
Fig. 4.—Fourth layer, continuous submucous and subcutaneous suture. No. 1 chromic catgut.

The ends of the sutures are left long until after the placenta is delivered. I prefer to operate while the placenta is separating because it shortens the anesthesia and lessens blood loss. It also removes the temptation for meddlesome interference in the third stage. Exceptionally the placenta separates before the operation is completed, but the uterine bleeding can be controlled by an assistant or nurse pressing on the abdomen below the uterus so as to lift it up into the upper part of the abdomen. The only serious objection to repairing the perineum in the second stage occurs in those rare cases when one has to remove the placenta manually. When this happens one has to place an additional row of stitches to restore the perineum to its former condition.

At first I thought that the expulsion of the placenta would loosen the sutures, and I would test each one to see if it could be drawn more tightly. I have never found one loosened except when I had to introduce my hand into the uterus to deliver the

placenta. The sutures are cut flush with the skin, a solution of bichloride of mercury is poured over the vulva, a pad is applied and the patient is put back to bed.

Except when there has been a third degree laceration, the aftercare is the same as if there had been no sutures. The patient is allowed a general diet and sits up whenever she feels like it. Rarely does the patient ever mention ''stitches.'' If the sphincter ani has been injured, the patient is kept on a liquid diet for five days. On the sixth day the patient is allowed a soft diet and is given an oil enema, if the bowels have not moved already. No further special care is given.

The present report is based upon 617 immediate repairs of the perineum. Most of them were episiotomies. Some were first and second degree lacerations. In one instance I had to deliver the placenta manually, and in doing so I damaged the repair to such an extent that I had to put in two additional rows of sutures. There was one-third degree laceration.

The evaluation of the results is based upon the condition when the patient was discharged from the hospital and upon the post-partum examination some four weeks later. Five hundred and fifty-five patients came back for a post-partum examination. Two repairs, or 0.3 per cent, broke down. The first of these was repaired with stainless steel sutures on the fifth day and a primary union resulted. The second case was that of a 28-year-old primipara who was sent into the hospital after a long tedious labor in her home. There was a constriction ring which failed to relax with adrenalin. Twenty-four hours later the patient was delivered by Braxton Hicks' version. An episiotomy was done at the first attempt. It was repaired twenty-four hours later. The wound broke down on the second day. As the patient was running a temperature of 103° F., it was thought best not to operate again. The wound healed by granulation in four weeks, leaving a broad scar, a small defect at the vulval ring, but a good thick perineum. I cite this as the worst end-result in over a thousand cases. Two patients had small patches of granulation tissue, one in the upper end of the wound and one in the lower end. In one the granulation tissue had disappeared at her second post-partum visit. I have not seen the second patient again, but when I heard from her she had no complaints.

Twenty patients had a cystocele of some degree. Ten of these had the condition before delivery and 10 developed it subsequent to delivery. This is a reflection upon the management of labor rather than on the perineal repair. Two patients had rectocele on admission. No attempt was made to correct this condition when the laceration incident to the current delivery was repaired.

Twice a strand of catgut, some three inches in length, was extruded from the anus, and was cut off. It made no difference in the end result as in both cases the union was perfect. In both patients a deep episiotomy had been done and both bled freely. In taking the deepest layer of sutures, the needle must have entered the bowel. This is easy to do and some authors recommend introducing the index finger of the left hand into the rectum to guard against such an accident. This always seemed to me a messy thing to do. From my experience with these two cases, it would seem to be an unnecessary complication of technique.

DISCUSSION

An immediate repair of the perineum is always accompanied by considerable swelling of the tissues. If sutures are tied tightly enough to bring the edges of the wound into apposition, the next day they will be cutting and constricting the tissues. This is both painful to the patient and inimical to healing. If the sutures are tied more loosely one may not get primary union. In other words one must tie the sutures so loosely that the edges of the wound must just come in contact on the second day, a nicety of judgment I was never able to acquire. When the sutures are laid longitudinally, a good anatomic repair is secured, and if no knots are used, the sutures adjust themselves to the subsequent swelling and keep the divided tissues in apposition without constriction or interference with the blood supply. A knot in a perineal suture means pain for the patient.

A simple method of avoiding knots has been described. The results with this method have been almost uniformly excellent. The repair broke down for a considerable extent twice in 617 cases. The final result in both cases was good. Twice there was a small superficial gaping of the wound less than a centimeter in length which was closed by a little tuft of granulation tissue, which in time disappeared.

Such a method requires practically no aftercare. If the sphincter ani is involved a liquid diet is prescribed for five days and an oil enema at the end of that time.

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MEDICAL ARTS BUILDING

SUBURETHRAL ABSCESSES, URINE POCKETS AND DIVERTICULA IN THE FEMALE URETHRA*

WITH A REPORT OF EIGHT CASES

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DIVERTICULUM of the female urethra, once considered rare, is now a not unusual diagnosis after careful gynecologic or urologic examination. Over a hundred cases have been reported, and these are rapidly being added to. Many names are applied to the disorder, e.g., urethrocele, cyst, abscess, urinary pocket or pouch. However, they are not to be confused with abscesses or cysts of Skene's glands, vaginal cysts or small vaginal myomas. Urethral diverticula may be classified either as true or false. When all the layers of the urethra are involved in the process, they are called true diverticula. False diverticula are those in which only the submucosa and mucosa protrude, the muscularis having ruptured.

Hohne,[1] Fromme,[2] Jarecki,[3] and Johnson[4] believe the origin of these defects is congenital in nature. Hence, they may arise from Gartner's duct, cysts formed by faulty union of primal folds, cell rests, Wolffian ducts, or vaginal wall cysts. To support his theory, Johnson reports the occurrence of a urethral diverticulum in a newborn female child. Most authors favor the acquired theory. Diverticula, they think, are the results of injury to and infection of the urethra. According to Huddy[5] and Cabot and Shoemaker[6] there are no glands in the posterior two-thirds of the female urethra. This portion corresponds to the region in the male urethra, situated between the vesical neck and the uterus masculinus. This is a very uncommon site for outpouchings in the male. Hohne suggests that paraurethral ducts analogous to the prostate gland in the male, may open into the female urethra and later become diverticula. Furniss[7] thinks filling and emptying enlarge them. Ensuing infection leads to abscess formation and rupture into the urethra. This communicating opening may persist, giving origin to a diverticulum. Childbirth surely introduces serious changes into the urethra as a result of pressure, tearing, pulling, stretching, and instrumentation during delivery of the infant. Probably every urethra is damaged to a greater or lesser degree following vaginal birth.

Diverticula may occur in women who have not borne children. Here, trauma of coitus, congenital structural weakness, infection of the urethra must be considered as the causative factors.

The symptoms produced by urethral diverticula are directly referable to the genitourinary tract. Pain, urinary frequency, and burning are nearly always present with this condition, but involuntary loss of urine is the most annoying symptom and is quite constant. Bloody urination is an associated symptom in a few cases. A swelling noticeable to the patient is an infrequent symptom. The diagnosis of urethral diverticula is based on careful examination of the urethra and vagina. A history of urinary difficulty, associated with involuntary soiling together with the discovery of a collapsible bulge in the vagina over the urethra, leads to the suspicion of diverticulum. If urine can be expressed from the mass into the urethra after the bladder has been emptied by voiding or catheterization, the diagnosis is made even without visual intra-urethral examination. The diagnosis is absolute after direct visualization of the diverticulum opening on urethroscopic examination. The pocket may also be filled with opaque material and then examined by x-ray. Skene's abscesses are excluded by reason of their location. Solid tumors or cysts do not collapse with pressure.

The treatment of choice in this deformity is surgical removal of the diverticulum. The anterior vaginal wall is dissected free over the site of the diverticulum as in the repair of cystourethrocele. The sac can be dissected free of surrounding structures. The sac is opened so as to expose the urethral communication. That portion of the urethra with the duct and its sac are amputated. The urethra is repaired by inter-rupted sutures, placed so as to have a transverse urethral repair. The technique of cystourethrocele is then followed to close the vaginal defect. An indwelling catheter is left in place for a period of ten days. Electro-coagulation of the duct and sac is not advised. Suprapubic drainage is uncalled for except in complicated cases.

CONCLUSIONS

1. Diverticula of the female urethra are not rare.

2. Structural weakness, trauma and infection are important etiologic factors in acquired diverticula. Congenital diverticula are disputed.

3. Symptoms of urethral diverticula are referable to the genitourinary tract. Their diagnosis is simple. Corroboration is easy by urethroscopic and x-ray procedures.

4. Treatment should be surgical extirpation. Suprapubic cystotomy is usually unnecessary. Electrocautery is dangerous and may result in poor end results.

CASE REPORTS

CASE 1.—Mrs. M. H., white, female, aged 52 years, was admitted June 17, 1929, complaining of urgency, hematuria, and a periurethral mass for two months. Menses began at 13 years of age, regular every twenty-eight days, and lasted three days. Dysmenorrhea until first child. Menopause July, 1921. Married 33 years. Para ii, gravida iii, children 31 and 29 years of age, living and well. One spontaneous mis-

carriage between. First delivery by forceps with second degree tear; second normal. Repair of cervix and perineum at 26 years. Curettage and radium November, 1928, for postmenopausal bleeding.

Physical examination negative except for vaginal findings. Perineum scarred; second degree cystocele. One inch from urinary meatus was a walnut-sized mass which fluctuated and, on pressure, pus escaped from the urethra. Cervix and pelvic viscera were negative. A diagnosis of periurethral abscess was made and on Feb. 18, 1929, an incision was made through the vagina to drain the mass. On Feb. 22, 1929, examination revealed the pocket again filled and a large amount of pus was pressed through the urethra. March 6, 1929, examination revealed an abscess about the size of a small marble with a sinus opening into the posterior portion of the urethra 1.5 cm. from the internal meatus. The cavity was again opened and thoroughly cauterized with the actual cautery. A retention catheter was inserted in the bladder and the urethra reconstructed around the catheter. Patient was discharged March 23, 1929. At present patient has no symptoms but the entire one-third of the urethra is missing due to the slough following the above procedures.

CASE 2.—Mrs. V. V., aged 26 years, para 0, gravida 0, married 2½ years, was admitted Feb. 11, 1933, complaining of occasional vague pains in the pelvis since marriage, never severe or constant. Her husband, a physician, examined her and diagnosed a cyst of the anterior vaginal wall.

Physical examination on admission was negative except for the bimanual findings. The vagina admitted one finger. The cervix was nulliparous. Uterus in good position, of normal size. The adnexa were negative. Speculum examination revealed an erosion of the cervix but no cyst was demonstrable. The patient was instructed to return for further study and on March 5, 1933, upon re-examination a walnut-sized, cystic mass was found on the anterior vaginal wall at about the middle third of the urethra. On further pressure the mass disappeared, clear fluid escaping through the urethra. A diagnosis of urethral diverticulum was made and on March 10, 1933, the cyst was resected. Sections of this 3 cm. cyst with a smooth internal lining and pale white fluid contents, revealed the cyst to be lined with flattened epithelium and covered on one side with stratified squamous epithelium.

CASE 3.—Mrs. C. R., aged 37 years, gravida iii, para i, two induced abortions, was admitted Nov. 29, 1937, complaining of a thick white discharge from the urethra for the past year. Patient consulted her physician who found ++++ albumin in the urine and prescribed a diet and medication. Urinary frequency and nocturia of 4 to 10 times persisted. Patient noticed that for one week before menses coughing or straining caused her to soil her clothing.

In 1922 pelvis was fractured in two places. Curettage was done eight years ago for bleeding after second abortion. Physical examination was negative. On bimanual palpation a bulging mass was found in the anterior vagina. Pressure on this mass caused pus to exude from the urethra. Pelvic examination was otherwise normal except for a multiparous cervix and a slightly relaxed perineum. Cystoscopic and urethroscopic examinations on Nov. 30, 1937, revealed a fistula of urethra in the posterior one-third. It was impossible to pass a urethral catheter into the opening but pus could be seen to exude when pressure was made in the vagina. On Dec. 10, 1937, resection of diverticulum was done.

CASE 4.—Mrs. G. W., aged twenty-six years, gravida ii, para 0, was admitted March 9, 1938, complaining of a mass in the vagina which increased and decreased in size. Patient had been under care of a physician for past two years, being treated for a cyst. Three years ago at the time of her last miscarriage she was told she had a cyst but had no symptoms and therefore did not return for treatment. During the past two years she has had a dysuria, straining and burning in nature.

Examination revealed an egg-sized mass in anterior vaginal wall. Pressure upon this mass causes pus to exude from the urethra. The introitus and vagina otherwise negative. Cervix firm and closed. Fundus in anteposition, normal size. Adnexa negative. Vagina bathed with a milky discharge. Urine examination: ++++ albumin; ++ pus and blood. Kahn: negative. March 12, 1938, operation.

Pathology.—Specimen consisted of a previously opened cystic mass measuring 3.5 by 2.5 by 2 cm., and contained single cysts up to 15 mm., lined by a purplish gray, granular tissue. Section of cyst in periurethral region revealed a markedly thickened wall composed of dense connective tissue and bundles of smooth muscle tissue. The wall was heavily infiltrated by lymphocytes and a few polymorphonuclear leucocytes. The inner lining was composed of a thick layer of stratified squamous epithelium. Complete recovery.

CASE 5.—Mrs. S. S., aged 45 years, para i, gravida i, was admitted Oct. 7, 1938, with the following complaint: painful bearing-down feeling with dripping, with urge and marked frequency of urination and great difficulty starting for twenty-five years and especially severe during past two months. Incontinence and a mass in vagina below urethra for two months. There were also some backache and constipation.

Cystoscopic examination Oct. 10, 1938, revealed a normal bladder. A fistula was found on the posterior wall of the urethra. This appeared infected and pus would exude when pressure was exerted from within the vagina. On Oct. 14, 1938, this mass was resected through the vagina and found to be an infected diverticulum of the urethra about one-half inch from distal opening.

Microscopic Diagnosis.—Dense and loose fibrous tissue covered in part by non-cornifying stratified squamous epithelium. In one area deep in dense connective tissue was a portion of what was apparently a sinus tract containing pus and with chronic inflammatory reaction in its wall. No pocket lined by epithelium was noted.

CASE 6.—Mrs. M. D., aged 41 years, was admitted Aug. 28, 1938, complaining of backache, lumbar and sacral, for two years since birth of last child; coccyx fractured during delivery. She had had dysuria for three years, stress incontinence four years, and pyuria and hematuria for five to six years. A right oophorectomy and appendectomy were done in 1921. Seven years ago she received a fractured skull and a possible pelvic fracture in an accident.

She had been married twenty-two years. Para iii, gravida iii. Instrument with first labor. Pressure on a plum-sized mass attached to urethra, caused pus to exude from urethra. Cystocele and rectocele. She had an eroded cervix with retention cysts.

The diverticulum was dissected free and the duct excised. Urethra was repaired and cervix amputated. A cystourethrocele was repaired and vaginal wall closed. Patient left hospital on tenth postoperative day in good condition.

CASE 7.—Mrs. A. H., aged 48 years. Incontinence for three to four years, with dribbling and bed-wetting. Gravida i, induced abortion; para 0. In 1926, salpingectomy; 1937, vaginal plastic; 1938, operation for repair of urethrovaginal fistula.

Examination.—Normal female except for abdominal and vaginal scars and local pathology which consisted of essentially a bulge in the anterior vaginal mucosa just below urethra and 0.5 cm. from urethral meatus. Pressure caused urine to exude from urethral meatus. Cystoscopic examination revealed normal bladder. Urethra presented a small opening in posterior wall 0.5 inch from meatus, which communicated with the vaginal swelling.

Diagnosis.—Urethral diverticulum.

At the first operation an attempt was made at closure which resulted in urethrovaginal fistula, at the second operation the fistula was dissected and closed, with healing and was otherwise intact.

CASE 8.—Mrs. L. R., aged 35 years, para 0, was admitted Jan. 22, 1939. Pregnancy, sixteen years ago, terminated by induced abortion at two months. Complained of pain in vagina and had had vesicle tenesmus for five years.

Perineum and buttocks showed scars from previous fistulectomy. Vagina admitted two fingers. There was a plum-sized mass on anterior vaginal wall. Cervix, uterus, and adnexa were negative. Cystoscopic: Urethra was elongated and reddened. One-fourth inch from the internal meatus was an opening, from which pus exuded on pressure to mass in vagina.

Past History.—Nov. 17, 1938, fistulectomy. At this time there was acute urinary retention. On examination a mass was found in the vagina, and catheterization relieved the condition. Kahn test was found negative. The patient was operated upon on Jan. 28, 1939.

Complete healing and freedom of symptoms have been obtained in each case.

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DISCUSSION

DR. EUGENE A. EDWARDS.—Eight similar cases of urethral diverticula and pocketing from our service have been reported by McNally.

There is one case that warrants description—a patient with a calculus in a true diverticulum. This woman gave a two-year history of a severe backache, later of pain in the vagina, especially marked on sitting down. There was occasional hematuria and incontinence of urine. Urethroscopic examination and x-ray showed the stone, probably a calculus in an already formed diverticulum.

Five of our patients gave a history of previous pelvic infections. Only four had had full-term pregnancies. This might indicate a relation between Skene's duct infection and periurethral abscess as a causative factor.

The diagnosis of these pathologic lesions around the urethra is not difficult. The diagnosis of seven of our cases was made by the gynecologists, but I cannot agree with Schmitz that the treatment of urethral conditions is a gynecologic problem. I feel that they belong in the field of urology.

DR. C. W. BARRETT.—I have seen a few of these cases. I have found no great difficulty in curing them by simply opening the urethrovaginal wall, dissecting out and tying off the sac. The gynecologist is in a better position to treat this lesion than the urologist, for it frequently requires some supporting operation with which the gynecologist is more familiar.

DR. J. DUANE MILLER, GRAND RAPIDS, MICH.—Occasionally when these lesions are not readily palpable, the patient may be treated for a considerable period of time for chronic urethritis without permanent relief. Under these circumstances, investigation with contrast media will often show a small diverticulum, the removal of which will result in a cure.

DR. SCHMITZ (closing).—Most of our cases were in multiparas and at least 50 per cent were due to injuries at childbirth. I think, therefore, that these injuries are out of the realm of the urologist.

I agree with Miller that after other possibilities have been investigated it is necessary to have x-ray examination with contrast medium to isolate the opening of the diverticulum.

Speert, Harold: The Passage of Sulfanilamide through the Human Placenta, Bull. Johns Hopkins Hosp. **63:** 337, 1938.

Sulfanilamide, given by mouth to pregnant, full-term women during labor, passes readily to the fetus, the concentrations of both the free and acetylated forms acquiring equilibrium between the fetal and maternal bloods within approximately five hours. The drug also passes rapidly into the amniotic fluid.

C. O. MALAND.

A PRACTICAL TREATMENT OF GONORRHEAL ENDOCERVICITIS

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PUERTO ARMUELLES, PANAMA, C. Z.

THE introduction, within recent years, of artificial fever therapy, pelvic short wave diathermy, the Elliott treatment, and sulfanilamide saturation, have produced a confusing period of transition in the treatment of gonorrhea in the female. The present study seeks to emphasize a modification of an older and better understood approach to this problem: cauterization or fulguration of the cervix and its subsequent treatment. I am aware that improvement in heat therapy or sulfanilamide-like compounds may already have reduced some of the objections to these recourses. A simple, practical method of treatment, which may usually be conducted in the office, is herewith presented. It has yielded gratifying results in my hands.

Because the cervix is the principal focal point of gonorrhea in the female and the only one presenting a formidable barrier to eradication of the disease, consideration of its treatment defines and limits this clinical summary.

CAUTERIZATION OR FULGURATION OF THE CERVIX

In contrast to the generalized systemic action of fever therapy and chemotherapy is a direct attack upon the deep-seated glands harboring the gonococcus in the endocervix. The futility of topical applications in this area was recalled by Notes[1] who reported only 8.7 per cent cures from the use of local antiseptics, and 19.3 per cent cures following one or two cauterizations of the cervix in dispensary patients. He adds "no patient who cooperated failed of cure." Following cauterization, Notes applied silver nitrate 25 per cent solution to the cervix once a week to stimulate local reaction and promote drainage. Apparently, arrest of disease required about a year.

I advocate a modification of this method. The cervical canal is cleansed, swabbed with 5 per cent mercurochrome, and anesthetized with a 5 per cent solution of diothane and 5 per cent benzyl alcohol in 55 per cent alcohol, applied on cotton wrapped applicators. Care is exercised *not* to pass the applicator, or the cautery, beyond the resistance encountered at the internal os. Anesthesia is usually adequate in ten minutes; if it is not, the cauterization had often better be done under a general anesthetic. If the canal is narrow, it is first gently dilated. Either the Post cautery or Paquelin cautery may be used; if the former, with incisive radial strokes, for the latter with a gentler touch. A thorough cauterization of the mucosa of the endocervix should be attempted. Repetition will not often be necessary.

The patient has been instructed that following or quite independently of cauterization, she may develop a pelvic infection. She is advised to go immediately to her home, and to remain in bed for two days. Throughout the entire course of treatment, she is instructed to do no active housework, to abstain from alcohol, exercise, dancing, and coitus; fatiguing social activities, prolonged shopping tours and sustained walking or standing are also interdicted. Observance of these restrictions constitutes the best safeguard against pelvic extension, which has occurred in 20 per cent of our cases.

On the second day following cauterization, the patient reports for aftertreatment. In the dorsal position, with speculum in position, a low pressure cleansing douche of potassium permanganate, 1-2000, is given. The vagina is dried, and a small gauze sponge placed beneath the cervix. A tightly twisted cotton tipped applicator is

dipped in pure phenol and introduced into the cervix, any surplus being carefully removed with alcohol. The gauze pad beneath the external os protects the vaginal mucosa. It is then lifted with forceps and by exerting gentle pressure used to dry the cervical canal. Treatment is carried out daily, with 25 per cent silver nitrate solution, and pure formalin used on succeeding days, in rotation with phenol.

The effect of these potent antiseptics is to induce an intense local tissue reaction in the cervix. This is characterized by marked edema, redness and abundant sero-sanguineous discharge. Gonococci extruded upon the surface of the canal by this tissue response are destroyed by the antiseptic application of the succeeding day. If exposure of the cervix presents no unusual difficulty, the treatment is attended by little, if any, pain. Interruption of daily cleansing and antiseptic application is not permitted during the menses. Increased blood flow through the affected parts during this period is thought to emphasize the indication for destruction of gonococci on the surface of the cervical canal. We have not observed a greater incidence of pelvic extension during or after the menses in individuals so treated.

Smears or cultures for gonococci are made once or twice each week. One will be disagreeably surprised to encounter the organism after weeks of treatment. Two or three successive negative reports permit cessation or reduction of office treatment.

After withdrawal of the antiseptic applications, swelling and inflammation of the cervix subside, the slough separates, and a healed, healthy canal is produced. Dilatation of the cervix, including the internal os, is now carried out with sounds. This should be repeated twice at intervals of one and two months to assure patency. It has not been found that this method of treatment induces stenosis of the canal, except in certain instances in which the infection is extremely acute at the time of the cauterization. The average time required for daily treatments has been from six to eight weeks. Cure has resulted in all cases presenting full cooperation.

COMPLICATIONS AND CAUSES OF FAILURE

Inadequate cauterization is the principal defect of technique. The light, radial "strokes" of the cautery used for nonspecific erosion and endocervicitis do not suffice, since the deepest glands must be exposed to ensure eradication of gonococci. Cauterization should be temporarily withheld in extremely acute infections with marked edema of the cervix and profuse discharge. Inability to secure adequate exposure of the cervix, and incomplete topical anesthesia, call for a short general anesthetic agent. Should marked bleeding occur during cauterization, the operation is best terminated at once. A dull red cautery tip may seal the bleeding point. Failing this, the cervical canal is swabbed gently with a saturated solution of potassium permanganate for hemostasis, and the vagina packed. Moccasin venom or whole ovarian extract may be injected. In the uterus undergoing fibrous involution, annoying hemorrhage is unfortunately not uncommon. In such instances, a second attempt at cauterization should not be made for a week or longer. A recurrence of hemorrhage will then force abandonment of the cautery procedure. Widespread pelvic infection following cauterization, reported by Cannell and Douglass,[2] has not been observed in greater degree than that of spontaneous extension of pelvic inflammatory disease occurring in untreated or conservatively managed gonorrhea. Attention must be called, however, to the possibility of bladder injury.[3] It is my impression that this accident cannot occur if the operator is at all times conscious of the exact position of the entire cautery blade, and its heat potentiality. The implication is that the cervical canal must be sufficiently wide to admit the cautery without "forcing." This frequently entails preliminary gentle dilatation as far as, but not beyond, the internal os. Elongation and thinning of the cervix in procidentia demand extra caution.

FULGURATION VS. CAUTERIZATION

If the cervix is to be fulgurated, the monopolar current should at present be selected. Appraisal of the deep tissue injury inflicted by the bipolar cutting currents is too uncertain to risk perforation of the cervix, bladder, or uterus. I have found a satisfactory instrument in the Jarosch cervical electrode with unipolar energy. Its shank prevents passage through the internal os. The greater heat penetration of

fulguration should be especially efficacious in dealing with a gonococcal infection. This advantage is apparently offset, however, by the added difficulty in estimating the tissue-effect. of fulguration as compared to that of the electric cautery. My experience is that the results obtained are identical; in the fulguration cases there has been a slightly higher incidence of subsequent pelvic infection.

RÉSUMÉ

1. A satisfactory method of treating gonorrheal endocervicitis consists of one- or two-stage cauterization or fulguration of the cervix followed by daily application to the cervical canal of phenol, silver nitrate solution, and formalin.

2. Adequate saturation with sulfanilamide-like compounds (neo-prontosil, uliron) may advantageously precede and follow the cauterization.

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UNITED FRUIT CO. HOSPITAL

AN UNUSUALLY LARGE TUMOR OF THE VULVA*

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FIBROMAS and fibromyomas of the vulva are comparatively rare. That a tumor of the vulva should have been allowed to grow to the size of the one here described is almost incredible.

Leonard[1] in a report on ''Fibroma and Fibromyoma of the Vulva'' in 1917 noted their rarity when he stated that in 23,000 gynecologic admissions to the Johns Hopkins Hospital, there were but 6 cases of fibroma. Nearly all fibromas showed degenerative changes if they were allowed to develop for too long a time, and 22 per cent showed malignant changes (14 out of a series of 64). Vascular changes and swelling were noted at the time of menstruation and pregnancy.

The patient was a colored woman, Mrs. A. Y., aged 28 years, admitted to the Gynecological Service of Sydenham Hospital on May 2, 1938.

History.—In 1929, the patient noted a mass on the vulva about the size of a walnut. Urination was not interfered with nor was menstruation affected. This mass was excised in a hospital in Savannah, Ga. Six months later, while making her home in New York, she noted that the mass had reappeared. In November, 1930, she was admitted to Kings County Hospital where a biopsy was done and she was discharged with the diagnosis of papilloma of the vulva.

Since that time, the mass gradually became larger and in the six months preceding admission grew to such an enormous size that walking was impossible without supporting the tumor in a sling. Urination on admission to the hospital was only possible when the patient stood up and lifted the tumor. Defecation was not interfered with. Menstruation ceased September, 1937. No bleeding occurred from the tumor although a slight discharge was noted from the mass for several weeks preceding admission.

The patient's record showed a 4-plus Wassermann reaction at Kings County Hospital in 1930, and she received several courses of intravenous and intramuscular injections.

*Presented at a meeting of Section on Obstetrics and Gynecology, of the New York Academy of Medicine, March 28, 1939.

There is a history of a bubo in the right groin discharging pus, and necessitating incision when the patient was fifteen years of age.

At the vulva there was a mass 11 inches in diameter, 23 inches from symphysis to anus, pedunculated, involving both labia majora and minora and the other structures of the vulva, extending from the symphysis pubis to the anus. The tumor was firm, attached to the overlying skin and showed a number of sinuses discharging pus. The vagina could not be entered except with the tip of a finger, while the urethral orifice was completely surrounded by the tumor.

Laboratory Findings.—Urine: Specific gravity, 1.025; albumin, 2-plus; sugar, negative; hyaline casts, 5-8 per field; white blood cells, 5-8 per field; Hg, 40 per cent; red blood count, 2,800,000; white blood count, 7,100; polymorphonuclears, 47 per cent; lymphocytes, 50 per cent; monocytes, 3 per cent; Wassermann, negative; Frei test, positive.

The patient was under observation for one week and during this time the local infection was treated by the use of daily antiseptic dressings.

Fig. 1.—Photograph taken two days before operation, May 7, 1938.

On May 9, under avertin anesthesia, the tumor was excised. A rubber catheter was inserted into the bladder and left in situ throughout the operation. The incision was made completely encircling the mass, as for a vulvectomy, so that it extended along the symphysis around both labia and met underneath at the urethra, having the appearance of a double V. The tumor was dissected from the underlying tissue and bleeding was controlled by grasping the bleeders with clamps and coagulating them with the bipolar coagulating current. To relieve tension the skin was undermined and a counter incision was made along the symphysis. The skin edges were then approximated with interrupted silk sutures. An indwelling mushroom catheter was placed in the bladder.

Postoperative course was uneventful except that immediately following operation, the patient went into moderate shock which, however, responded readily within twelve hours to stimulative treatment. The sutures were removed on the eighteenth day and although the skin edges had separated, there was no infection present. The raw areas healed by secondary intention and the patient was discharged on June 15, 1938. Healing was not complete until six weeks later and photographs show how the raw areas became completely epithelized during that time.

After the removal of the indwelling catheter, urination became normal. On return to the follow-up clinic the patient stated that she menstruated normally and has continued to do so regularly. She further reported that she was able to resume normal sexual relations. The patient at present is normal in every respect except for the absence of both labia majora and minora and some local loss of skin pigment.

Pathologic Report.—(Dr. Arthur A. Eisenberg.)   Gross specimen weighed 5,000 gm. (11 pounds) and measured 13 by 10 by 9 inches.   Skin is coarse and has several areas of pigmentation.   The tissue is firm and on section is somewhat whorled. The whorls are located around softer areas 2 by 6 cm.   The entire right portion has a gray white surface, but the softer areas are pink.   The left portion is succulent with a small amount of connective tissue.   A large amount of fluid escapes from the cut surface; this fluid coagulates on standing.

Histologic Report.—There is present a pale, fibrous, collagenous tissue with an admixture of what resembles myxomatous tissue, although the latter is not at all prominent.   The tissue is rather vascular with both medium and small sized vessels. The former occasionally show considerable thickening of the wall due to medial thrombosis, but the intimal changes are not prominent.   There are numerous areas of edema and irregular spaces between the fibers.
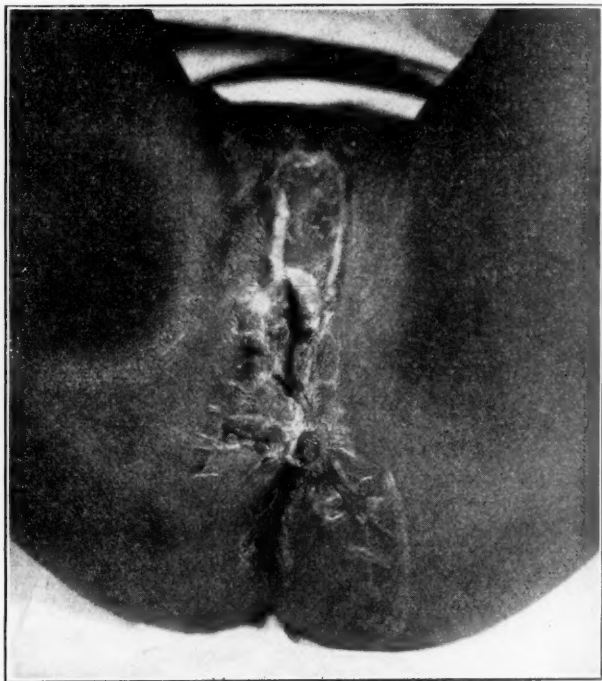
Fig. 2.—Photograph taken June 13, 1938.

The striking features are widely scattered small and large collections of chronic inflammatory cells and granulomatous tissue, of which at least half of the cells are plasma cells and the remainder lymphocytes, mononuclears and occasional leucocytes. These cells are arranged both perivascularly, particularly around lymphatics, but also without relationship to vessels, i.e., wherever skin tissue is found.   There is no histologic evidence of malignancy; occasionally an area containing muscle tissue is noted.

Apparently the tumor is essentially a fibroma, with a slight admixture of myxomatous and myomatous tissue, which has slowly grown to large proportions and because of its dependent position has exerted pressure on the vessels, especially the lymphatics, to produce a widespread edema.   The presence of so many inflammatory cells and granulomatous tissues points to a widespread irritation which is both marked and continued, although its exact nature remains unknown.

Although the preponderance of fibrous tissue justifies a diagnosis of fibroma of the vulva, the presence of so many inflammatory cells and the abundance of granulomatous tissue might be due to lymphopathia venereum or to a syphilitic infection. However, a definite choice between these two diagnoses is impossible, as the history and laboratory records could support either thesis. We therefore feel that the future progress of this patient will be the clarifying factor regarding the relation of syphilis or lymphopathia venereum in this growth.

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44 EAST 78TH STREET
430 EAST 86TH STREET

VAGINAL REMOVAL OF REPEATED ECTOPIC PREGNANCY*

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EARLY diagnosis and removal by the vaginal route of ectopic pregnancy has become an established procedure in many American and European clinics. It is rather unusual to find patients who have developed an ectopic pregnancy for the second time. It is still more unusual to have the opportunity of treating a patient in whom recognition of an ectopic pregnancy, twice within a period of three years, could be accomplished in the early stages and vaginal removal of both of the fetuses performed.

Mrs. L. S. (No. 315732). The patient was admitted to the Presbyterian Hospital, April 7, 1936 on the medical service. At that time she was 32 years old, had been married sixteen years, and had one child twelve years before. This child was stillborn at term due to a spina bifida.

The complaints on this admission were relative amenorrhea of sixty-two days' duration. During this time, there had been only two days when slight vaginal bleeding was noticed. Excessive fatigue had been present. Aching through the pelvis had become more pronounced. The morning of admittance severe right-sided pelvic pain had occurred. At that time the erythrocytes numbered 4,650,000 and the leucocytes on repeated examinations ranged from 6,900 to 10,300. The patient was discharged from the hospital on April 9, 1936 and readmitted on the gynecologic service April 20, 1936. The patient thought she had menstruated April 13 and 14. There were no complaints. There was a tender palpable mass in the region of the right adnexa and the Zondek test was positive.

Operation was performed April 20, 1936, and an ectopic pregnancy of the infundibular portion of the right tube with several large blood clots was removed through a posterior colpotomy incision. The ectopic sac measured 5½ by 3½ cm. The opposite tube and ovary were grossly normal. The uterine scrapings were not profuse and histologically revealed only a moderate decidual reaction. The convalescence was entirely normal and the patient left the hospital on the seventh postoperative day.

The patient was admitted to the hospital again Aug. 25, 1938, complaining of a weak feeling in the region of the vagina and a brownish vaginal discharge of one week's duration. This spotting had begun at the time she had expected her regular menstrual period. There had been no amenorrhea. There was slight pain in the left lower quadrant. No enlargement or uterine changes could be palpated on vaginal examination. There was a definitely increased tenderness in the region of the left Fallopian tube. The patient was undecided whether her symptoms resembled those of her previous experience. The examination of the

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blood was quite normal. The hemoglobin was 92 per cent (Dare), erythrocytes 5,150,000 and the leucocytes 10,600. A pregnancy test of the urine was not advised.

Operation was performed Aug. 26, 1938. The posterior cul-de-sac was opened without difficulty, and there were no adhesions caused by the previous vaginal operation. There was no free blood in the peritoneal cavity. An ectopic pregnancy 1½ cm. in diameter was removed from the middle portion of the left tube. Due to the patient's intense desire for a pregnancy and with her consent previously obtained the proximal one-third of the patent tube was left in place. The convalescence was uneventful and the patient left the hospital on the fifth postoperative day, rather doubting, as she expressed it, that anything had been done to her.

This patient's past obstetric history combined with the occurrence of repeated tubal pregnancy is interesting from the standpoint of possible etiologic factors. Her first marriage had occurred sixteen years before. During the second year of this marriage, which lasted only three years, she had given birth to a full-term stillborn baby. This stillbirth was due to a marked fetal abnormality, the main item of which was a marked spina bifida. She had been married four years the second time before the first tubal pregnancy occurred.

It would be rather an unusual circumstance that both husbands should have such a defective germ plasm as to produce three defective pregnancies. This triad might suggest that the primary difficulty was ovular and that the two ectopic pregnancies were the result of a more pronounced fetal defect than the one which interfered with closure in the spina bifida. It might also suggest that this defection was also a progressive one.

55 E. WASHINGTON STREET

RUPTURED INTERSTITIAL PREGNANCY AFTER SALPINGO-OOPHORECTOMY ON THE SAME SIDE

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IT IS a well-recognized fact that interstitial pregnancy is uncommon as indicated by the studies of Lavell,[1] who reports but 12 such instances out of 410 cases of ectopic pregnancy at Bellevue Hospital and Wynne[2] who found an incidence of 1.66 per cent interstitial out of 2,405 collected cases. Even rarer, however, is the interstitial pregnancy which follows on the same side on which a salpingectomy has been performed previously. Among those reporting such cases are Lesse,[3] Nache,[4] Hofmeier,[5] Di Palma,[6] D'Errico,[7] Deutsch and Clahr,[8] and von Schroeder.[9] However, the rarest condition encountered is ruptured interstitial pregnancy occurring on the same side on which previous salpingo-oophorectomy has been done. I have recently encountered such a case and after an extensive search of the literature have found only seven others identical with it, and these are reported by Richardson,[10] Campbell,[11] Douglas,[12] McIntyre,[13] Meyer,[14] and Naujoks[15] (2 cases). One must be careful not to be misled by reports of cases in which a stump of the isthmus of the tube has been left in which subsequent pregnancy has occurred.

M. L., aged 35 years, negress, was operated upon Jan. 10, 1937, at Barnes Hospital by the resident gynecologist for ruptured ectopic pregnancy in the ampulla of the right Fallopian tube. Right salpingo-oophorectomy was performed, and in addition a pedunculated myoma 2½ inches in diameter which was arising from the right cornu of the uterus was excised.

The patient was readmitted to Barnes Hospital Jan. 12, 1939 on the general surgical service with a diagnosis of partial intestinal obstruction made by the referring physician.

Previous to the first operation the patient had had 3 miscarriages, 3 abortions, and 3 normal deliveries, and 4 months subsequent to it she became pregnant and had a normal delivery in February, 1938. Her last menstrual period began Dec. 5, 1938 and about three weeks later she began to notice occasional nausea. Jan. 8, 1939 she was seized with terrific pain in the lower abdomen and became extremely weak. No vaginal bleeding occurred. She was put to bed and in a few hours began vomiting. A physician was called whose treatment consisted of repeated enemas. Pain, vomiting, and abdominal distention persisted up until the time of admission to the hospital on the fourth day of the illness.

Physical Examination.—The patient was a moderately obese, 37-year-old negress who was acutely ill. Temperature 37° C., pulse 100, and blood pressure 96/40. The abdomen was markedly distended and tympanitic, presenting a subumbilical, midline operative scar. There was moderate muscle guard over the entire abdomen and likewise marked tenderness to light pressure, particularly over the lower abdomen. Neither visible nor audible peristalsis was present, and heart sounds were not heard over the abdomen. Upon vaginal examination the cervix was perhaps slightly softened, the fornices not bulging; however, the patient was so exquisitely tender that nothing further could be learned. Rectal examination gave no additional information.

Laboratory Findings.—White blood count, 18,700; red blood count, 3,410,000; hemoglobin, 65 per cent. Urine contained albumin 1+, diacetic 3+, and numerous casts.

I regarded ruptured ectopic pregnancy with resultant paralytic ileus as the most probable diagnosis. The patient was prepared for operation with parenteral fluids and continuous gastric siphonage for several hours.

Under general anesthesia, a low left rectus incision was made, and upon exposing the peritoneum, it was apparent that there was a large amount of free blood beneath it. Upon opening and inspecting the peritoneal cavity, the left Fallopian tube and ovary were found to be entirely normal, but hanging loosely from the region of the right uterine horn was an ovisac about the size of a golf ball and from the deep depression remaining in the horn, active bleeding was taking place. The ovisac, containing a 1.5 cm. embryo, was removed and the horn closed with several rather deep-locked stitches of chromic catgut. The medial superior portion of the broad ligament was tacked over the raw surface of the horn. The body of the uterus was about twice normal size and softened. A Penrose-drain was placed in the bottom of the pelvis, after as much free blood and clots as possible had been removed, then routine closure was carried out. Five hundred cubic centimeters of citrated blood was given during operation. The patient was kept on continuous gastric siphonage for three days postoperatively, until peristalsis had become re-established, and her recovery was uneventful.

DISCUSSION

This case is of interest for at least three reasons: It is extraordinarily rare, there being only 7 identical, authentic cases previously reported. We were confronted with a difficult diagnostic problem in explaining the cause of the obvious paralytic ileus of four days' duration. The case opens up a field for speculation as to where the ovum became fertilized, and how it became implanted in the interstitial or mural portion of the tube on the same side on which salpingo-oophorectomy had been performed previously. The existing possibilities are that the ovum from the remaining left ovary passed down the left tube into the uterine cavity and then entered the uterine orifice of the right tube stump, having been fertilized at some point along this course, or else the ovum migrated across the peritoneal cavity to enter a patent right tube stump, being fertilized either in the peritoneal cavity or in the stump.

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ENDOMETRIOSIS OF THE ROUND LIGAMENT SIMULATING HERNIA

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ENDOMETRIOSIS in its protean manifestations gives rise to a confusing clinical picture at times, and it is the purpose of this paper to record an instance of rather unusual site of endometrial tissue.

Endometrial tumors or "implants" as Sampson calls them have rather widespread distribution within the peritoneal cavity, commonly involving the ovary, the peritoneum, the rectovaginal septum, etc. Less frequently they occur in the umbilicus, in the round ligaments and in laparotomy scars. The method of extension of the process to the round ligament and inguinal region is as much in dispute as the etiology of endometriosis in general. The lesion of the round ligament may consist of a more or less solid tumor, an adenomyoma, or may be in the nature of a hemorrhagic cyst. The frequent association of hernia and inguinal endometriosis has been a matter of comment with several writers. Errors in the differential diagnosis between hernia and inguinal endometriosis are not infrequent. Cullen who described the first case of inguinal endometriosis in 1896 thought his patient had a hernia; likewise Sampson, Schmitz, Christopher, Neel and others made similar errors.

Involvement of the intraperitoneal portion of the round ligaments gives rise to no important symptoms; involvement of the extraperitoneal portion does. With endometriosis of the round ligament usually a tumor of the inguinal region occurs; this may be either cystic or solid; it may or may not be painful; it will disappear when the patient lies down, if it is the cystic type, and there may be an impulse on coughing; the solid type of lesion as a rule is not reducible.

From this brief description it becomes apparent how inguinal endometriosis may readily be mistaken for a hernia.

CASE REPORT

The patient was a 34-year-old female who had never been pregnant, although married for twelve years. She complained of a "bunch" in the right groin of five years' duration. At times this "bunch" would ache, but it became most painful during menstrual periods. In addition there was a "bunch" in the left groin but this one never pained; both of these disappeared when the patient lay down. This patient had commenced to menstruate at the age of 13 but was very irregular until age 18, when she established a twenty-one-day cycle with each period lasting seven days and being moderately profuse. Until five years ago there had been no pain at menstruation; at that time pain made its appearance and has gradually increased until now it is severe enough to necessitate opiates for relief. The last period had terminated two days prior to examination. There was no history of bladder or rectal disturbance. The past history was irrelevant except for attacks of paroxysmal tachycardia.

Examination disclosed a well-nourished and well-developed individual. The abdomen showed some tenderness in both lower quadrants. No masses were made

out in the inguinal regions while the patient was on the examining table. Bimanual examination revealed a retroflexed, adherent uterus, about twice normal in size. There were tender masses in both fornices. With the patient standing, a soft, easily reducible mass made its appearance in the right inguinal region; the mass transmitted an impulse on coughing; the left inguinal region revealed no mass and no impulse on coughing.

At operation, the usual picture of rather extensive endometriosis was found. The uterus was enlarged and densely adherent to the rectum. The left tube and ovary were firmly attached to the posterior aspect of the fundus. The serosal surface of the uterus and the pelvic peritoneum were studded with typical endometrial implants. The broad ligaments showed old and recent hemorrhages. There were hemorrhagic cysts of both round ligaments, the one of the right side being considerably larger. The latter was about 7 cm. in length and 2 cm. in diameter. The appendix was buried in the right side of the pelvis with its tip involved in the endometrial process. A panhysterectomy with removal of both tubes and

Fig. 1.—Section from left round ligament showing hyperplastic endometrial acini in typical endometrial stroma. The stroma contains recent hemorrhage. ×60.

ovaries, both round ligaments and the appendix was done. The cystic round ligaments were dissected out as completely as possible through the internal rings. The patient's postoperative course was uneventful except for a prolonged attack of paroxysmal tachycardia, and she left the hospital on the sixteenth day with the wound healed. Final examination of the patient was made fifteen months after operation at which time nothing of note was found; the "bunches" in the groins had not returned.

Laboratory Report.—The specimen consisting of the entire uterus, tubes, and ovaries, weighed 260 gm. The myometrium of the fundus contained several leiomyomas, the largest of which was 2.5 cm. in diameter. The endometrium was thickened and polypoid but showed no gross invasion of the muscle. The right tube was grossly normal. The right broad ligament was thickened and hemorrhagic. The right ovary measured 4 by 2.5 by 1.5 cm.; it contained a hemorrhagic corpus luteum and simple follicular cysts. The left broad ligament was markedly thickened and indurated and contained areas of old and recent hemor-

rhage. The left tube was markedly thickened; the left ovary could not be identified. A separate structure consisting of a thin walled cyst containing serosanguineous fluid was present.

Microscopically there were found in both broad ligaments, numerous foci of endometrial tissue with acini containing recent and old blood. The distal end of the appendix showed endometrial implants with dense scarring. The endometrium of the fundus uteri showed benign hyperplasia. Sections of the nodules of the myometrium showed the typical histology of leiomyoma.

For the microscopic study of the tissues, the author wishes to thank Dr. John J. Clemmer, Director of the Laboratory.

302 STATE STREET.

CAVERNOUS HEMANGIOMA OF OVARY IN A GIRL TWELVE YEARS OF AGE

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VASCULAR tumors are common on the skin and mucous surfaces, occurring on the head, neck, trunk and extremities. However, visceral vascular tumors are rather rare, only a few cases being reported in the literature, these tumors originating essentially by proliferation of vascular walls or from a matrix of angioblasts. The cavernomas are characterized by irregular blood spaces lined with endothelium, and formed by a connective tissue stroma. The growth may appear as a diffuse mass, but more often as a circumscribed tumor, having a distinct capsule. Visceral angiomas usually occur in the form of cavernomas. Such cavernomas were reported by Rosenthal, Langer and Keene, occurring in the liver. Cases have also been reported where cavernomas have occurred in the spleen and in the alimentary canal, of which there are about 20 cases described in the literature. Cavernomas of the ovary are rather rare since not many have been reported. J. P. Shearer reported a case in a child 3.5 years old. R. Keller reported a case in a woman 36 years of age. In 1927 R. H. Jaffe, reported a case of multiple hemangiomas of the skin and internal organs. Our case is a cavernoma of the left ovary occurring in a girl 12 years of age.

Patient, R. C., 12 years old, gave a history of having pain in the pelvis for the past two weeks. The pain was more or less continuous, and, at times, of a twisting character. During this time she had nausea and vomiting. Constipation was present and enemas were not effectual. She had one period prior to the onset of this condition, but a regular menstrual cycle was not yet established since the patient was only 12 years old. However, she was seen by several doctors and one made a diagnosis of pregnancy, in view of her amenorrhea. On admission to the hospital her temperature was 99.6° F., and pulse 92. A complete blood count showed: Red blood count, 3,950,000; white blood count, 9,200; hemoglobin, 12 gm. The differential count showed polymorphonuclear leucocytes, 78 per cent; and lymphocytes, 32 per cent. The Schilling count was as follows: segmenters, 74 per cent; stabs, 4 per cent; juveniles, 0 per cent; myelocytes, 0 per cent. Urinalysis showed a trace of albumin, no sugar, and the microscopic examination revealed 8 to 10 leucocytes to the high power field.

Physical examination showed a rather tall young girl for her age, but she appeared undernourished and somewhat emaciated, probably the result of her two weeks' illness. Her features were pinched, showing evidence of constant pain. The abdomen was flat and tenderness was elicited on palpation over the whole hypogastric region. No masses could be felt in the abdomen by external palpation and no rigidity was present anywhere over the abdomen. A rectal and vaginal examination

was made under nitrous oxide and oxygen anesthesia. The hymen was very much relaxed so that a small speculum was easily inserted. The vaginal mucous membrane was somewhat congested and a small amount of mucopurulent discharge was present. The cervix was eroded. A smear of the cervical and vaginal secretion was negative for gonococcus. On bimanual examination the cervix was hard to the touch, the uterus was small, hard and anteflexed. A large mass the size of a grapefruit was present in the pelvis and more in the left adnexa. A diagnosis was made of ovarian cyst, probably with twisted pedicle, because of the severe pain. On the following day under ether anesthesia the abdomen was opened and a large ovarian cyst twisted on its pedicle was found on the left side. The cyst was easily separated from adjacent tissues but incorporated the tube. A left salpingo-oophorectomy and appendectomy was done. The cyst was about 12 cm. in diameter and hemorrhagic in color.

The histopathologic report was as follows: *Gross:* Specimen was apparently a large cyst with an attached Fallopian tube and an appendix. The appendix was 3.5 cm. long and 0.8 cm. thick. The wall of the appendix was thick, mucosa edematous and formed one-half the wall. The lumen was very narrow. The cyst was multilocular, contained a sanguineous fluid; one portion of the wall at its thickest region was 1.8 cm. thick and composed apparently of a blood clot. The Fallopian tube was filled with blood down to the cyst and its thickest region was 2.0 cm. *Microscopic:* The tissue labeled ovarian cyst was composed of numerous large and small blood vessels with no intervening supporting tissue. The blood vessels were filled with red blood cells. Periserosal tissue adjacent to the cyst was edematous and was infiltrated with inflammatory cells, mostly plasma cells and pulp. These sections were covered so densely with red blood cells that no underlying tissue could be seen.

Diagnosis.—Cavernous hemangioma of ovary with diffuse hemorrhage.

5505 SPRUCE STREET
5012 SPRUCE STREET

APPARENT CONGENITAL ABSENCE OF UTERUS

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(From ''The Clinic'')

COMPLETE congenital absence of the uterus or of the vagina, or of both, has been reported by daCosta,[1] Veach,[6] and Walters and Qualls.[7]   It is exceedingly unlikely, however, that there was an absolute absence of all vestiges of these parts. Graves[3] and Wharton[8] emphasize that there is always some rudimentary tissue present even if it exists only as a fibrous band.

The following case of apparent absence of the uterus was operated upon by one of us (C. M. B.) on April 20, 1939:

CASE 1.—R. L., an eleven-year-old Korean girl, was admitted to The Children's Hospital, Honolulu, for removal of an interval appendix.

A right rectus incision was used and, following the removal of the subacutely inflamed appendix, it was noted that the broad ligament of one side swept across where the uterus should have been and fused with its fellow from the opposite side of the pelvis. No thickening was present which might have been interpreted to be the uterine body. The tubes and round ligaments were joined in the midline and were unusually well developed for a girl of eleven. The ovaries were also normal and prominent. Subsequent vaginal examination through an otoscope revealed no apparent cervix, and on rectal palpation, no uterine body could be felt. Nothing was done other than appendectomy and examination of the pelvic contents. Convalescence was uneventful. Aside from the congenital anomaly, this girl looked like any normal female.

In addition to the foregoing, we would like to mention three other cases of aplasia of the uterus which have come to our attention during the past three years.

CASE 2.—R. F., Portuguese, aged 23 years, came to one of us (H. E. B.) June 4, 1937, for treatment of a Bartholin's abscess of gonorrheal origin. Vaginal examination revealed a total absence of cervical os, and no uterine body could be felt. Intravenous pyelograms were done to see whether any congenital malformation of the kidneys might also be present. The films showed no left kidney shadow, while the right kidney shadow was normal. Nothing further was done at this time.

On Aug. 1, 1938, she was operated upon by Dr. R. J. McArthur at Wailuku, Maui, for the relief of lower abdominal pain. At laparotomy, two rudimentary uteri were found, one on each side of the pelvis. The left uterus and oviduct were represented by a small tube with an ostium corresponding to the fimbriated end of a Fallopian tube. The embryonic uterus coursed downward along the free edge of the broad ligament gradually disappearing in the vicinity of the bladder in a small fibrous cord. The right uterus was similar to the left, only larger, had no ostium, and appeared to be large enough to menstruate. Both uteri were excised. The ovaries were left alone as they were normal except for some small cysts which were punctured. A constricted appendix was removed. Recovery was uneventful.

CASE 3.—Mrs. M. C., aged 26 years, Portuguese, complained of vague pain in the abdomen. Incidental vaginal examination revealed no visible or palpable cervix or uterine body. She stated that she had been operated upon by Dr. W. T. Osmers of Wailuku, Maui, in 1926, for acute appendicitis. Although hospital records have been lost, Dr. Osmers writes that he remembers a very rudimentary uterus was found, consisting merely of a small knob. The ovaries were small but recognizable. Other details are lacking.

CASE 4.—A nurse, aged 23 years, German-Portuguese, single, tall, masculine type, flat breasted, was operated upon by Dr. C. L. Phillips of Hilo, Hawaii, for acute appendicitis.

At operation, an inflamed appendix was removed. Pelvic inspection revealed nothing resembling a uterus. Two small rudimentary tubes were joined in the midline along with two poorly developed round ligaments, giving the appearance of a complete supravaginal hysterectomy. There was a very small, buttonlike piece of tissue in the vaginal vault which seemed to represent the cervix. No true ovarian tissue was seen, though it was believed that a slight thickening at the end of each tube may have been ovary.

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AN IMPROVED METHOD FOR APPLYING PELVIC HEAT
USING AIR

Louis B. Newman, M.D., Chicago, Ill.

IN USING any device for producing heat in any part of the body, two very important requirements must be fulfilled in order to treat the patient safely and effectively without the danger of burns and their associated effects. First, the maximum tissue temperature at any time during the treatment must be known, and, second, the point or area of maximum heat concentration in the tissues must also be known.

A new improved apparatus for producing dry heat has been developed by the author, and has been used for several years in the treatment of pelvic inflammatory conditions. This machine (Fig. 1) fulfills the requirements stated above. With it,
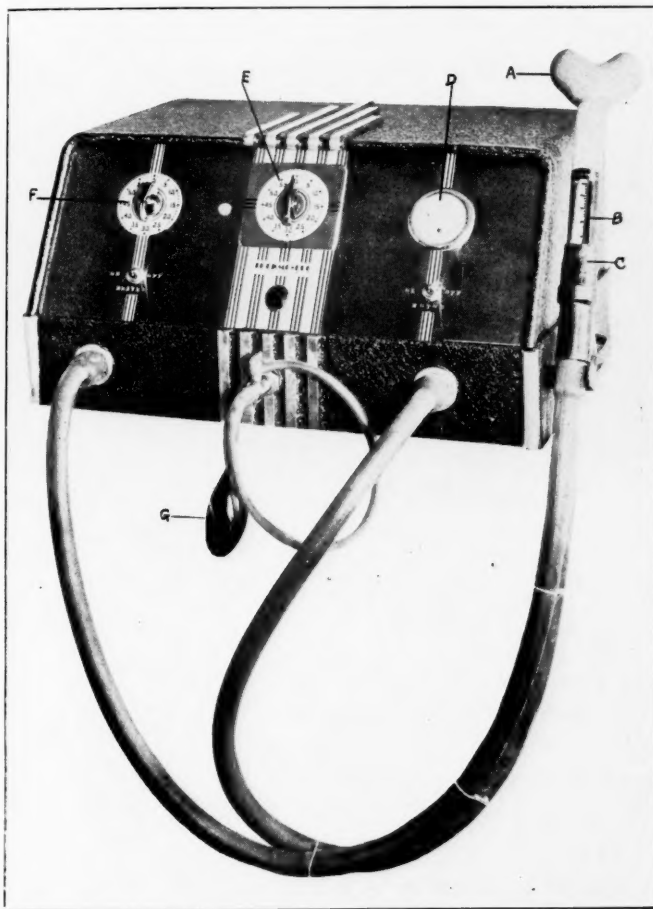

Fig. 1.—*A*, Bag; *B*, thermometer; *C*, applicator; *D*, pressure gauge; *E*, time clock; *F*, temperature control; *G*, rubber bulb.

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heated air is circulated through a special shaped thin-walled rubber bag which is inserted in the vagina in a collapsed state and then inflated with air so as to distend the vagina. This distention of the vagina serves a two-fold purpose, first, the tissues are "ironed-out"; all of the folds and rugae are flattened, thereby bringing the rubber bag in immediate contact with the tissues, and, second, due to this fact, the heat is radiated uniformly over a large area to the surrounding structures thereby eliminating so-called "hot spots."

The heated air is continuously circulated through the bag producing a uniform temperature throughout and an even distribution of the heat. Therefore the maximum tissue temperature during any time of the treatment is never higher than the temperature recorded by the thermometer which extends into the bag. The maximum heat concentration instead of being over a small area will be uniform over a large area in direct contact with the applicator bag. Any other type of electrode which is used in the vagina without producing distention of the cavity will only have point contact, or at best, a small area of contact with the tissues, thereby resulting in the possibility of the heat concentrating at this spot and producing a burn.
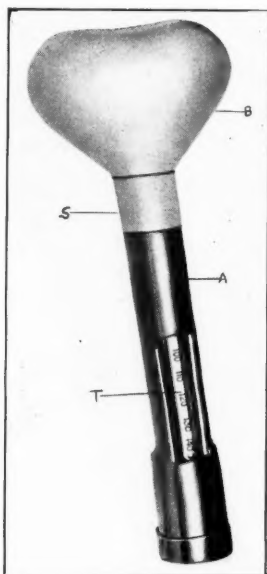

Fig. 2.—*B*, Bag; *S*, sleeve; *A*, applicator; *T*, thermometer.

The machine is small and consists essentially of a fan which circulates air through the applicator bag. The air is heated by an electrical unit, the temperature being controlled automatically by a thermostat set for any desired temperature. Temperatures up to 130° F. can be used, although lower temperatures for longer periods of time seem to be more beneficial. The thermometer which extends into the bag (Fig. 2) is protected by a bed of rubber. Broken thermometers can be readily replaced. A hand-operated rubber bulb similar to that used on blood pressure machines is used to inflate the rubber bag, thereby giving any degree of smooth and even distention. The pressure which is approximately 1 to 1.5 pounds is indicated on the pressure gauge. A time clock is incorporated in the machine so that the treatments can be timed for any desired period.

Inasmuch as the bag is distended with air and since the weight of the contained air and bag is negligible, being less than 0.25 ounce, there is no pressure or feeling of weight in the pelvis to produce any discomfort to the patient during the treatment, as there is with a bag filled with water, the weight of which is approximately 0.5 pound. Observations and reactions of patients disclose a marked feeling of in-

crease in the weight of liquid-filled bags as the treatment progresses. This sensation is not experienced when the air-filled bag is used. If the bag should tear during a treatment, the patient will not be burned, as the bag merely collapses; there is no escape of hot water. A double seal sleeve is incorporated on the applicator so that torn bags can be easily and quickly replaced, no cementing being necessary.

The technique in giving treatments is very simple. The deflated bag is lubricated and inserted into the vagina. The bag is then inflated by means of the rubber bulb, the amount of distention being governed by the comfort of the patient. A pillow placed under the patient's knees also supports the applicator holder so as to eliminate any pull on the pelvis. The time clock is set for the length of treatment, the temperature control is set for the desired temperature, the switch is turned "ON" and the treatment is begun. No preheating is necessary as the air in the bag at the beginning of the treatment is never lower than room temperature and will not chill the patient. During operation, the air is heated rapidly to the desired temperature As the volume of air increases when it is heated, the bag will expand slightly and thereby result in more perfect contact with the surrounding tissues which, by this time, have become softer and more pliable due to the heat. If the patient complains of too much distention, a little air is permitted to leak out by opening the air valve on the pressure bulb. At the end of the treatment, the switch is turned "OFF," the bag is deflated and withdrawn from the vagina. There is nothing to spill or leak to burn the patient or soil the bed. The applicator holder together with the bag and specially constructed thermometer (Fig. 2) can be sterilized as a unit, either by boiling or immersing in a suitable antiseptic solution. By using an additional bulb, a massaging effect can be obtained if desired.

When the applicator is removed, the machine may serve as an excellent source of dry-heated air which can be used for therapeutic purposes.

With this machine, uniform dry heat together with distention may be safely given to both the male and female pelvis over long periods of time. The maximum temperature and the area of maximum heat concentration are known at all times during the treatment. This, coupled with the ease of operation, insures a high degree of safety, efficiency, and comfort to the patient. By circulating air through a cooling coil, low temperatures may be secured in the rubber bag.

5146 WEST 25TH STREET

Howkins, J. and Brewer, H. F.: Placental Blood for Transfusion, Lancet **1:** 132, 1939.

The authors were able to collect an average of only 47 c.c. of placental blood in 50 consecutive cases of normal labor. Twenty-two per cent of the collections were contaminated when checked for sterility at intervals of six to fifteen days. The organisms found were *B. subtilis, B. coli, Staph. albus,* and *B. pyocyaneus.* The ordinary personnel of the labor ward was used in the collection. The writers conclude that this source of blood is uneconomical and unsafe.

CARL P. HUBER.

Halbrecht, J.: Transfusion With Placental Blood, Lancet **1:** 202, 1939.

The author reports 116 transfusions of blood obtained from 520 placentas at the Beilinson Hospital, Palestine. Four reactions occurred of which 3 consisted of a chill and 1 of dyspnea and tachycardia. Blood preserved in 3.8 per cent solution of sodium citrate stored at 4 or 5° C. for as long as fourteen days was used. An average of 50 to 60 c.c. of blood was drained from each placenta with a maximum of 160 c.c. The results are equal to those obtained with fresh blood and placental blood is looked upon as an important source of blood for transfusion.

CARL P. HUBER.

Editorial

American Congress on Obstetrics and Gynecology

THE first American congress devoted to this branch of medicine was held in Cleveland, Ohio, from September 11 to 15. Its success may be measured by the attendance and the countrywide contributions to its program. The paid membership totaled over 2,500, but the total number of persons who attended the session and visited the exhibits was probably well over 5,000. Physicians, nurses, public health workers, hospital administrators and educators crowded the various meeting rooms and exhibition halls and there were many expressions favorable not only to the present enterprise but to its continuance in future years. The program included over 120 papers presented in sections devoted to medicine, nursing, public health, hospitals and education, and each of these conducted round table discussions. There were also five joint afternoon sessions and an equal number of evening meetings open to the general public.

One of the primary objects of the Congress was to bring together all interested groups and the large attendance furnished ample proof of the scope of this interest. It was remarkable that so many workers, eminent in their various fields, could be brought together at this initial gathering and that so many outstanding contributions were made available to those who came to Cleveland on this memorable occasion. Individual references to the many addresses are impractical but the general summary of the work of the Congress presented on another page by its General Chairman will afford an insight into its important accomplishments.

Great credit is due to the executive committee of the American Committee on Maternal Welfare, which promoted the Congress and to its Chairman, Dr. Fred L. Adair, as well as to the various sectional groups, for the excellent arrangements which made of this gathering an outstanding contribution to the advancement of American obstetrics and gynecology. The participating organizations are to be commended likewise for their material support and similar commendation must be extended to the commercial exhibitors and to those who made the scientific and technical displays of such value and of such high standards.

The Congress will go down in American medical history as a signal accomplishment which, it is hoped, may be repeated at definite intervals.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY*

GENERAL SUMMARY AND COMMENTS

FRED L. ADAIR, M.D., GENERAL CHAIRMAN, CHICAGO, ILL.

THE groups assembled at this first congress on obstetrics and gynecology had a common purpose and were actuated by a motif for the prevention and correction of conditions which lead to the disability or death of mothers and their babies. They were gathered here to promote those conditions of living which are inherent in our institutions and in our human rights; that is, the equal opportunity for life, liberty, and the pursuit of happiness. It is our belief that there are two fundamental objectives which are closely coordinated and are essential to the attainment of these goals. We might state succinctly that without proper physical, intellectual, and psychical health, there is no satisfactory education, and without such education about ourselves there cannot be optimum health.

Past as well as existing episodes, individual as well as group tragedies, personal as well as impersonal experiences, national as well as world cataclysms bring forcibly to mind the importance of having fewer abnormal, more normal, and an abundance of superior personalities.

Democracy and civilization have no need for abnormally developed persons with perverted ideas and behavior. Democracy needs an abundance of normally, of socially and of humanistically minded individuals among its citizens. The world needs superior right-minded and great leaders who are capable of thinking through and of developing not only plans for national but also for international welfare. The foundations of the past were laid by our ancestors, the structures of the present were reared by our fathers. We are occupying what they and we have built. The bridges to the future over which those yet to be born must travel are being devised now. It is for us to see that those structures are so well planned that they cannot collapse and be swept away by rising torrents. The future depends largely upon what is done now. It is important for those of us who believe in our nation and in its institutions to recognize that the mothers and their babies are the first and last line of defense. We wish no one from within or from without to interfere with or to dictate the course of development of our institutions and our country. We have no desire to hinder other peoples who believe in differing types of development so long as they interfere in no way with our peace and our freedom. We can and should defend the mothers and babies, both born and unborn, to the last trench both in peace and in war.

* * * *

The laws of heredity and of environment are the most potent factors in the life of any individual. The father is an equal hereditary influence, but he has nothing to do with fetal environment except indirectly through the mother who determines the intrauterine life of the fetus. The newborn, the early and later infant and childhood life is largely influenced by maternal environment. Doubtless this is the most powerful and lasting influence which affects the development of our bodies, of our minds, and of our characters.

Years ago, measured by the individual duration of life, but minutes ago in terms of the development of human life, the idea was set forth that all men are created

*Presented at the closing session of the Congress, September 15, 1939.

For lack of space this address can only be published in part but will be supplied in full in the author's reprints.

free and equal. Free doubtless in our continent so far as human contacts and nature's laws permit, but, while politically equal in theory, at least they certainly are not equally endowed physically, mentally, or psychologically. We could all agree that among us everyone should be freed of avoidable hereditary and environmental handicaps, so that all could have as nearly as possible an equal opportunity and a fair start in life.

We all recognize this ideal in our sports which are governed by certain rules which enable us to compete on a fair basis, with an umpire enforcing the rules. In civil life there are certain laws, with the courts acting as the umpires. Unfortunately, the laws are not always equitable and work out unfairly, and our judges are not always unbiased. Government is an experiment and there are few valid controls; democracy is being tried and is slowly advancing to the goal of equal opportunity and the maximum of happiness, life, and liberty to all.

This introduction may seem far afield from the objectives of the Congress, but if one considers carefully what maternal care means, the purpose of these few comments is apparent. The basis of our life depends on equal opportunity for every one of us, and the future of our institutions and country depends upon the development of equality for all mothers and their babies. The accomplishment of this involves the control of both hereditary and environmental influences, all of which are not completely understood. Time will bring added knowledge, but in the meantime we have much to do in securing universal application of the knowledge which we already possess.

It has been conclusively proved that the more general application of the knowledge we possess to the care of mothers and their babies can and has reduced our national, state, and local mortality rates. However, it is necessary to emphasize again and again that a reduction of the mortality rates is only a partial answer to the problems. Death is a very concrete criterion upon which we can base certain factual data from which some conclusions can be drawn. The mortality rate is also an index of a larger morbidity rate which is of tremendous importance. Much disability and a shortened life of a mother or of a baby can be charged to the lack of proper obstetric care. Death is the natural sequence of life and all individual physical life terminates after a specified cycle. While we live, health is most desirable, and no one person and no society can look with equanimity upon life with avoidable illness or one ending in premature death.

The groups represented here are primarily concerned with health and with health education. The discussions and the data presented in our programs and by the movies and in the exhibits have portrayed certain information to us and to the public through the press and the open public meetings. These data may be classified into the following categories: The present status of our knowledge about the mother, the fetus, and the newborn; the present methods of applying this knowledge for the benefit of all; the revealing of possible errors and of definite gaps in our existing knowledge and the discussion of ways and of means to eliminate these errors and to discover the proper approach to the solution of unsolved problems have all been considered more or less fully.

There is the tremendous task of selecting the best methods of applying our present knowledge and of determining how these programs can be universally applied. In passing it may be well to observe that certain fundamental principles are well established and essential to the success of any plan and while the methodology or technique of application may vary, the basic principles remain unaltered. For example, no one could at present deny the necessity for clean aseptic deliveries, though there might be a difference of opinion as to the best means of preventing puerperal infection.

The groups represented here are doctors, nurses, public and voluntary health agencies, institutions for medical and nursing service and for education. Our common objectives are those that pertain to the welfare of women, chiefly mothers, and the babies, especially the newborn. Our objectives are ultimately the same though our approach, viewpoints, and methods of solution may differ. It is vital that we agree on certain fundamental principles, even though the methods of application and of accomplishment may differ. We could all doubtless agree that care of mothers and babies which is adequate to conserve individual and community health and life is essential.

What then are the fundamental principles which are necessary for adequate maternal and infant care?

We believe that preconceptional care is basic, and in using this term I should like to stress the point that preconceptional care is a preparation for conception and for reproduction. In discussing preconceptional care we cannot avoid a consideration of both eugenic and euthenic viewpoints. This type of care is not only maternal but also paternal. In fact, it is both parental and ancestral. Proper reproduction may not be so vital for the individual, but it is paramount for the survival and success of the human race. We have much to learn about heredity, especially of its application to the human being. We must move slowly but surely in applying the laws of heredity to the control of human reproduction, but certainly where the parents, particularly the mother, offer both a bad heredity and poor environment to the progeny, some method of artificial selection and control would seem advisable. Hereditary factors should receive proper consideration in evaluating the ultimate outcome of a future conception. The proper preparation for future propagation begins at or before birth as the health of future parents influences that of the progeny.

The prevention of diseases which interfere with skeletal and other tissue growth and with development of the infant and child's body and brain is essential.

The prophylactic measures which minimize the incidence and seriousness of organ and tissue damaging infectious diseases must be universally applied, not only to maintain the health of the individual but also in the interest of the future family and community.

Adolescence arrives with its accompanying phenomena and problems of which both the individual, the family and the community should have a sane appreciation. There must have been both antecedent education and character building of the maturing persons thus enabling them to withstand the biologic shock of this rapidly developing aspect of life. Habit forming of various kinds is to be avoided, especially the various forms of drug habits which are often detrimental to the individual and may be harmful to germ plasm. Illicit relations and pregnancies constitute important biologic and social problems which no generation has yet solved satisfactorily. Sane biologic education, character building, and the establishment of proper family ties seem to offer the best approach for the solving of this biologic equation. These matters are closely related to venereal disease control, the solution of which health problem is being vigorously attacked from many angles, one of which is that of maternal care.

This brings us to a most important phase of preconceptional care, the necessity of which has long been recognized by some in order to safeguard the health and lives of the coming generation. Premarital examination is an answer to many questions which arise in the minds of individuals contemplating marriage. Intelligent and careful examination and advice to these young persons will avoid many a contagion, some of which might damage or kill a future baby, and prevent the development of unhappy families and their possible disruption.

The prospective family will be safeguarded medically, economically, and sociologically. Legislation alone, even with attempts at enforcement, will not be completely successful without intelligent and wholehearted cooperation of both professional and lay groups. There must be a good understanding of the underlying principles and objectives and of the benefits to be derived. Many unhappy lives and homes can be avoided by these relatively simple medical and social preventive measures.

It is necessary to recognize that successful medical and nursing care in general as well as that of mothers and babies is dependent upon many factors, such as facilities available, and upon economic and sociologic status. Nutrition may for instance be of the greatest significance from the standpoint of maternal care, but doctors and nurses cannot furnish the actual foodstuffs. There are many elements which are fundamental for the good health of all and particularly for that of mothers and babies. Many conditions affecting the individual and the community are beyond the control of the professional groups here represented. We cannot build houses, furnish clothes, or supply the things necessary for proper personal and community nutrition and hygiene. All of these are basic for the care of mothers

and infants. For the mothers as they must supply the proper hygiene and nutrition not only for themselves but also for their infants especially during pregnancy and lactation.

The period of growth and development is vital as the fetus, newborn, infant, and child must have in addition to the materials essential for maintenance, those substances fundamental for growth. Growth is a process which is affected by both hereditary and environmental factors. Growth and development do not follow a straight line but a jagged one because of spurts which occur at various epochs in the life cycle. If essential elements are lacking at crucial periods, an arrest of growth may occur which cannot be compensated later. This means a permanent lack of optimum development. Interference with skeletal development and subsequent bony deformity due to lack of certain nutritive elements and of proper hygiene is one of the most striking illustrations which is obvious even to the casual observer. It is curious but nevertheless true that the availability of the essentials is not the only difficulty encountered in securing proper hygiene, food, etc., for mothers and infants. Habits and customs have such a strong hold upon our lives that many of us follow them blindly in spite of obvious errors and even though the proper hygiene and food are accessible. The problems then are not always simple and people have to be not only educated but re-educated. It is essential not only to remove factors leading to erroneous living but also to introduce a program of right living. In other words, one's life has often to be reconstructed and rehabilitated. This cannot in many instances be accomplished in one generation. If we do not worship our ancestors, we frequently cling to their customs and our own habits.

It might just as well be recognized that all persons are not well adapted for parenthood. In some instances reproductive life may be detrimental to a woman and hasten the inevitable end of her life. Under other circumstances the infant itself may be a poor product and be useless or harmful to itself and to others. It is also well known that fertility differs greatly in different persons and that some individuals are incapable of reproduction. This may be a great tragedy in their lives. Many can be made fertile—some remain sterile. Probably the greatest tragedy in a woman's life is the rejection of an opportunity to have a baby, and as a result acquire a permanent sterility but retain a longing for a subsequent childbirth. Much can be done now to cure infertility and more will be learned in the future.

Repeated or habitual abortions sadden many women's lives, but scientific advances in endocrinal therapy offer real hope to many for a successful pregnancy. The problem of abortion is a vast one, and no one really knows how many occur each year, but 750,000 is a not unreasonable estimate. The program of prevention is a very sizable one, and it can be solved only by proper education and medical care. The problem of abortion is much larger than the saving of the lives of 4,000 women and their lost pregnancies yearly. Many women are thus invalided and many become sterile. The care of patients having abortions is one of the important phases of prenatal care.

Prenatal care involves more than medical and nursing attention, as many sociologic and economic factors are related which doctors and nurses cannot solve. They, as well as others, need compensation for their work and unfortunately our present unbalanced economic system places many of our citizens in a marginal or submarginal economic status so that their income must be increased or supplemented. How these various difficulties can best be overcome no one has yet proved. An ultimate solution is essential and progress toward this goal must be made as rapidly as possible. Adjustments in our economic and sociologic life which will promote education and health among us are vital for the continuation of our democratic institutions and country. It can be reiterated that the success or failure of our civilization depends largely upon our ability to progressively improve our mothers and babies physically, intellectually, and psychologically. This depends largely upon continuity of programs and plans. One step leads to another and thus preconceptional is followed by prenatal care. It is impossible to state the details of prenatal care at this time, but it is important to bring about a situation where every mother receives it in her home, in the clinic, or in the hospital as circumstances require.

The sequence of intra-partum care follows with the onset of labor whether it is premature, at term, or postmature.   The necessity for artificial stimulation of the onset of labor sometimes arises, but unless this coincides with the preparatory phase occurring at the end of gestation, an abnormal course of labor is likely to ensue. The conduct of labor requires great judgment and care and the paramount consideration is, of course, the safety of both mother and baby.   One may seem to be hard and callous at times in not yielding to the pleadings of patients and friends for relief or for a speedy termination of labor, but one has to be kindly sympathetic but never soft.   One cannot allow sentiment to overcome good judgment.

There is much said about radicalism and conservatism in obstetric practice. We should understand what these terms mean.   Operative procedures are a part of our treatment.   Medicaments are part of our armamentarium.   The same drug, as for example pituitary extract or ergonovine, may be used radically or conservatively.   By this I mean that in the one instance it may produce a casualty and in the other it may save a life.   As an illustration, these agents used radically during labor may provoke a uterine rupture or cause a fetal death.   When used rationally and conservatively their use may save a woman from post-partum hemorrhage.

The same statement applies to treatment by a surgical procedure which of itself is not radical as it is designed to be life saving.   Operations become radical when not justified or indicated and when the personnel and environment are not suitable.   A cesarean section may be conservative and life saving under one set of circumstances and irrational and radical in a different situation.   The same statement applies to other surgical procedures.   Even as relatively simple a procedure as the repair of a laceration, ordinarily considered conservative, might be radical under some circumstances.

Radicalism or conservatism is then based upon the result so far as the future life and health of the patient is concerned and not upon the procedure itself, provided, of course, the method is sound.

The completion of the three so-called stages of labor is followed by the dual problem of post-partum and postnatal care.   Both begin immediately, and at times a limited number of attendants may need to extend their ability and energy to the limit to give the proper care to both mother and baby.   These emergencies cannot always be foreseen and constitute one potent argument for institutional care where adequate equipment and personnel should be available.

For the mother the post-partum phase is a crucial period as she must recover from the analgesia or anesthesia, be protected from hemorrhage and possible infection, and have injuries repaired.   The immediate crucial period is over and the lying-in period follows with the involutional processes going on, the breasts beginning to function and her normal health and vigor being re-established.   Her subsequent life should be governed and supervised by her own good sense and that of her advisers who should be intelligently selected.   Follow-up examinations are necessary at intervals and unusual signs or symptoms should always throughout her remaining life lead her to find the cause by securing careful and intelligent examination and advice.   Every woman as well as man is exposed to the possible development of some disease which cannot be prevented by our present knowledge. Many of these may be remedied by early detection and treatment or their course favorably modified.   Cancer is one of these diseases.   The means of prevention are unknown unless susceptibility can be bred out of the human race.   Cure is possible, but this depends almost entirely upon early detection and treatment.   Time is too limited to even mention other conditions which with our present knowledge cannot be prevented or be cured.   Attention to the occurrence of any unusual or unexplained symptoms is necessary if the serious consequences of tuberculosis, of heart, and vascular or renal disease and of malignancy are to be avoided.

No one can replace a mother in the interest in her baby, and though intuition and maternal instinct are of great importance, they must be supplemented.   Mental attitude, proper training and education, the time, the opportunity and the resources are essential for proper motherhood and postnatal care.   This care begins almost before the process of birth is completed.   The prevention of injury and suffocation during labor are not always avoidable.   The baby may aspirate material as soon as

the head is born; this can usually be obviated. Warmth from the moment of birth is necessary for all but is vital for premature infants. Prevention of infection of the cord, the eyes, the skin, the gastro-intestinal tract, the nasopharynx, and the lower respiratory passages is necessary. Fluid and food, preferably breast milk, are, of course, essential. We have here considered particularly neonatal care as a phase of infant welfare which should go on with the thought that biologic principles govern the future of man.

In conclusion, it must be stressed that the care of mothers and babies should be a continuous process, each step leading inevitably to the next. The problem is greater than doctors and nurses alone can solve. It will require the cooperative effort of doctors, nurses, health workers, educators, scientists, administrators, sociologists, publicists, and the public to solve the problems surrounding human reproduction. Both private and public funds will be required to solve the problems and to carry on generally and successfully the necessary programs for the proper care of mothers and babies.

The practicing physicians, the nurses, the educators, the hospital administrators, and the public and the voluntary health workers who have assembled here at this Congress, the first of its kind, have by their effort, interest, and enthusiasm inaugurated this new cooperative movement which will bring us closer to our goal. I might outline the situation, now, as we end our meeting, in a few words:

1. Preconceptional care consists of the eugenic and euthenic preparation for marriage and reproduction. It includes proper growth and development from the beginning of life to maturity in all its phases. It is an essential factor in the elimination of disease and in the continuation and improvement of the human race.

2. Prenatal care is the attention given to the pregnant woman to maintain an optimum of health and comfort and to secure proper evolution of the pregnancy and development of the infant. This is accomplished by periodic evaluation of her health status for the early recognition of abnormal conditions, coupled with any necessary treatment, preventive or curative. It concludes with the necessary steps in the preparation for labor.

3. Intra-partum or delivery care, whether at home or in a hospital, requires the necessary physical setup, the essential equipment and trained personnel capable of giving competent maternal and neonatal care. It is vital that everything necessary to carry on routine care and to meet emergencies be available. It is not enough merely to save the mother's life, or to save the fetus; it is necessary to save both, and to leave them finally in a state in which they will ultimately be able to lead normal lives in the family and in society.

4. For the mother post-partum care is the next phase. It requires a period of rest and both medical and nursing attention. The mother must have proper hygiene and good nutrition. It is a period of recuperation and adjustment, during which essential routine care must be given and complications avoided or treated. The mother should be restored to normalcy with a desire and capacity for childbearing at the appropriate time, as well as being able to nurse and care for her infant.

Post-partum care should continue as a periodic supervision to maintain health, and to detect and treat any disease. Cooperation between the mother and her medical adviser is essential throughout life if serious illness is to be prevented or detected early enough to avoid serious consequences.

5. For the baby the postnatal care includes the immediate neonatal care and the more remote infant care. The baby should be examined promptly for any abnormalities and be supervised during early infancy and later life. Delicate adjustments are occurring during neonatal life and careful and capable attention is essential to maintain growth and development and to detect and treat variations from the normal.

It is to promote the best interests of mothers and their newborn babies that this Congress has been held. The solution of the varied problems involved in this objective is a task both national and local in scope, and it is only through understanding and cooperation of all agencies and individuals interested in these programs that progress can be made.

The health and lives of mothers and babies are most necessary for the integrity of the family and the welfare of the community. In a broad sense our problem is both biologic and sociologic, and it cannot be solved in the face of conflict between these fundamental sciences but only by a proper and cooperative understanding and effort.

The program of safeguarding these lives is much broader than its medical and nursing aspects. It has ethical, economic, and sociologic bases which can only be established and built upon safely by proper evaluation of all the factors and by cooperation among all those elements in the community which can be enlisted in the fight to save rather than destroy life. The enlistment is for the duration of this, our war.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY
MEETING OF MARCH 14, 1939

The following papers were presented:

Transvesicle Repair of a Vesicovaginal Fistula. Dr. Henry T. Burns.
Current Views on the Causation of Menstruation. Dr. Earl T. Engle (by invitation). (For original article, see page 600.)

CHICAGO GYNECOLOGICAL SOCIETY
MEETING OF FEBRUARY 17, 1939

The following papers were presented:
The Uterus Arcuatus. Dr. Frederick Falls. (For original article, see page 661.)
Indirect External Hysterography. Drs. Con Fenning (by invitation), M. Edward Davis and Fred L. Adair. (For original article, see page 670.)
Suburethral Abscesses, Urine Pockets and Diverticula in the Female Urethra. Drs. Herbert E. Schmitz and Peter A. Nelson (by invitation). (For original article, see page 707.)
Hydrocephalus and Spina Bifida Diagnosed by Roentgen Examination Before Labor. Dr. J. B. DeLee.

MEETING OF APRIL 21, 1939

The following papers and case reports were presented:
Prolapse of the Uterus, Hydronephrosis, Hypertension. Dr. Paul H. Wosika (by invitation) and Dr. Chauncey C. Maher (by invitation). (For original article, see page 684.)
Strictures of the Cervix. Dr. Hilliard E. Miller (by invitation) and Dr. E. Perry Thomas (by invitation).
Vaginal Removal of Repeated Ectopic Pregnancy. Dr. E. Allen. (For original article, see page 717.)
Reconstruction of a Bicornate Uterus Followed by Two Full-Term Pregnancies. Dr. A. E. Kanter.

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEETING OF APRIL 4, 1939

The following papers were presented:
Extra- and Intrauterine Pregnancy. Dr. David B. Ludwig.
Two Cases of Bicornate Uterus Associated with Pregnancy. Dr. James W. Stevenson.

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy and Disease

(Continued from September issue.)

Houel, J. E.: Acute Obstetrical Postoperative Parotitis, Bull. Soc. d'obst. et de gynec. 27: 231, 1938.

There is a great affinity between the salivary glands, especially the parotid glands and the genital glands. This explains the great frequency with which disturbances in the parotid glands occur in women because in them, interventions on the genitalia are frequent. Thus among 100 cases of postoperative parotitis, 75 will be in women and only 25 in men. In spite of this frequency among women, Houel has been able to find only seven cases of postoperative obstetric parotitis including one of his own. All of these cases occurred in women who had serious dystocia and prolonged labors which required operative intervention. Five of the women had cervical cesarean sections and 2 had been delivered by forceps. In not one of the cases was there a puerperal infection.

The treatment consists of catheterization of Stenson's canal. If this is not sufficient, surgical treatment must be used.

J. P. Greenhill.

Sheehan, H. L., and Murdoch, R.: Post-Partum Necrosis of the Anterior Pituitary, Lancet 1: 132, 1938.

Massive necrosis of the anterior pituitary gland is a relatively frequent finding in patients who die during the puerperium after a delivery complicated by collapse or severe hemorrhage. Patients who survive may develop a clinical syndrome, the main symptoms of which are absence or scantiness of the menses, asthenia, hypothermia, apathy, and sometimes weight loss.

In 54 cases investigated by the authors, there was no subsequent improvement in 12 cases showing genital atrophy. In the remaining 42, some recovery occurred in the majority. In 3 there was complete spontaneous recovery without specific therapy. There is nearly always a marked recovery if the patient becomes pregnant again. This usually appears early in the pregnancy and is permanent unless hemorrhage or shock is associated with the delivery. Occasional cases show no improvement as a result of pregnancy.

Case reports are given which show the improvement with subsequent pregnancy and illustrate the danger of relapse or even death from hemorrhage or collapse at delivery.

Carl P. Huber.

Mortara, F.: Contribution to the Study of Nervous Diseases in Pregnancy, Myasthenia Gravis Pseudo Paralitica, Riv. ital. di ginec. 21: 369, 1938.

The author feels that in a pregnancy complicated by a myasthenia gravis, interruption is almost always indicated. The medical management is rather difficult although symptomatic benefit may sometimes be had with the use of prostigmine.

Mario A. Castallo.

Zambonino, F., and Martines, S.: Report of a Case of Posterior Hypophysitis in a Pregnant Woman Characterized by an Infective Toxic Psychosis, Riv. ital. di ginec. 20: 193, 1938.

The authors present a fatal case of posterior hypophysitis in a pregnancy of eight months with symptoms of psychosis and hemorrhagic nephritis. They describe in full the clinical and histoanatomic picture.

AUGUST F. DARO.

Sheehan, H. L., and Murdoch, R.: Postpartum Necrosis of the Anterior Pituitary, Lancet 1: 818, 1939.

In a previous study the authors have pointed out that patients with an anterior pituitary insufficiency due to a postpartum necrosis of this gland can be cured symptomatically by a subsequent pregnancy provided that there are no serious complications at the delivery. They now report the successful treatment of such a patient in whom complete amenorrhea, menopausal symptoms, hyperinvolution of the uterus and increasing vaginal atrophy had been present since her fourth pregnancy at age 29.

The successful treatment was begun four and one-half years after the onset of symptoms. It consisted of the following over a period of 37 days: Days 1-37, progynon B in oil 50,000 I.B.U. every 2 days; days 21-37, proluton 5 mg. every 2 days; days 26-32, antex leo 100 mouse units daily (7 times). Bleeding occurred on the 31st day of therapy and continued for two weeks. Pregnancy was calculated to have begun 6 weeks after the course of treatment. Normal delivery resulted. The authors believe that the most probable explanation is that the extract of pregnant mare serum (antex leo) stimulated the development of follicles in the ovaries; that the resultant production of estrin maintained the hypertrophy of the genital tract previously produced by the injected estrin (progynon B); and the rupture of one of the artificially stimulated follicles liberated an ovum.

CARL P. HUBER.

Stern, S. I.: Pregnancy at Term and Cancer of the Cervix, Gynéc. et obst. 37: 295, 1938.

Pregnancy at term with coincident cancer of the cervix is rare. In nine years it was encountered only once among 14,000 births. Special interest is attached to this case report because it describes the spontaneous birth of a normal infant.

The patient, aged 38 years, para i, gravida ii, with a gestation approaching term came to prenatal clinic complaining of a foul, bloody, irritating discharge. Her previous gestation nine years ago had a spontaneous termination. On the posterior cervical lip and spreading to the vaginal vault there was a friable, exophytic tumor mass, 6 to 7 cm. in diameter, which bled on slight manipulation.

Approximately eleven hours after onset of labor the membranes ruptured. Cesarean section was planned, but a preliminary vaginal examination revealed complete cervical dilatation with the baby's head in the vagina. A 3,300 gm. male infant was born spontaneously. The amniotic fluid had a foul odor and a greenish tinge. No difficulty was encountered in the delivery of the placenta and the total blood loss was moderate. Though somewhat slow, the mechanism of labor was essentially normal and of a total duration of 16 hours. Except for some temperature elevation (37.2° to 38.3° C.) until the fifth day, the puerperium was uneventful. Uterine involution was normal. Speculum examination at the time of discharge revealed no change in the gross appearance of the tumor.

Histologic diagnosis of the cervical lesion was ''basal cell cancer''; of the placenta, ''hyalinization with placentitis.''

The favorable course of labor and its uncomplicated termination was attributed to the fact that the tumor mass did not penetrate deeply into the cervix. Despite the size of the baby no cervical tear resulted, and in the presence of a large focus of infection puerperal sepsis did not occur. The author reports that the patient

"is at this time in satisfactory condition," with a reduction in the size of the lesion following x-ray therapy. He is not specific concerning the patient's status, the length of time she has been under observation, or the details of her treatment.

A second patient, aged 33 years, gravida xii, had her last child 14 months previously. At two and a half months the present pregnancy was complicated by vaginal bleeding. The portio vaginalis of the cervix was found to be distorted by an ulcerating crater which bled readily. Under spinal anesthesia a Wertheim operation was performed with an uneventful postoperative course and primary healing. Two months after operation the patient's general and local condition was good.

ARNOLD GOLDBERGER.

King, Faust and Sanders: Intestinal Parasitic Infections Complicating Pregnancy, South. M. J. 30: 545, 1937.

During 6½ years, stool examinations were made on 3,290 white obstetric patients; in some instances, two or three specimens from the same patients were examined, so that over 5,000 careful examinations were made.

From an obstetric point of view, it is apparent that clinical amebiasis, especially if severe, might be serious complication. None of the patients presented serious symptoms, though in approximately one-half of them the presence of diarrhea or dysentery of variable intensity was noted. The authors agree with Craig that all individuals with amebic infection should be treated, and they see no objection to, and many reasons for, the treatment of pregnant women so infected. The authors know that their general health would be improved and they would not expect the occurrence of abortion or of premature labor as a result of the treatment. However, they were not able to treat many of the patients, owing to the fact that the large majority were in the ward for only a few days. It might be noted that the drugs most favored in management of this condition are chinoform, carbarsone and vioform.

Hookworm infection was found in 185 patients (5.6 per cent). It is apparent that a woman with this disease is handicapped to a degree corresponding to the intensity of the infection. This is due in great part to the anemia commonly found, with the concomitant lowering of resistance.

The authors had no case of abortion or premature labor as a result of treatment; on the contrary, they feel that such a termination is often avoided because of the improved condition of the patient following eradication of the infection. They prefer the use of tetrachlorethylene in 3 c.c. doses given in hard gelatin capsules on an empty stomach; a saline purge is given the night before and again two hours after administration of the drug. If ascaris is also present, hexylresorcinol is given at the same time. It is as necessary to treat the anemia as to eradicate the infection, and obviously this is particularly true in pregnancy.

J. P. GREENHILL.

Bolaffi, R.: Spontaneous Fracture During Pregnancy, Ginecologia 15: 593, 1937.

The author describes a case of spontaneous fracture of the maternal pelvis, without apparent cause, in a primipara seven months pregnant who was slowly walking in the street. Pregnancy proceeded normally and the healing process of the fracture studied by x-ray was normal. The delivery of a 3,350 gm. living fetus was also normal. The author emphasizes the rarity of this observation.

AUGUST F. DARO.

Szendi, B.: Morphologic and Biologic Changes Caused by Trichomonas Vaginalis in the Vagina of Pregnant Women, Arch. f. Gynäk. 162: 479, 1937.

Trichomonas vaginalis was found in the vagina of 44 per cent of the 200 women studied. There were no symptoms in about one-third, one-third showed a foamy discharge and the remaining group (30 per cent) had a definite vulvovaginitis with

inflammatory changes. The discharge is caused by an acute suppurating inflammatory reaction in the vaginal mucosa with vesicle and pustule formation. It is often characterized by a moldlike pseudomembranous coating followed by superficial ulcerations and an infiltration of the epithelial and subepithelial layers. The glycogen content of the vaginal mucosa is always greatly reduced. The trichomonas is never found in the tissue itself but lives on the cast-off debris. It lives in symbiosis with the bacillus of Doederlein and produces lactic acid. This accounts for the fact that the changes are relatively mild and also for the fact that many authors deny the pathogenicity of the trichomonas. This production of lactic acid actually inhibits the growth of other organisms even though the pathology produced makes the entrance of pathogenic bacteria easier. The trichomonas plays no role in the production of puerperal morbidity.

RALPH A. REIS.

Farias, L. L.: Appendicitis in Pregnancy, Bol. Soc. Chilena de obst. y ginec. 2: 171, 1937.

The author reports 13 cases of appendicitis complicating pregnancy observed in 1,129 pregnancies.

There were three deaths in this group: all had generalized peritonitis. Of the remaining 10, all went to term except one. The pregnancies were advanced from two to seven months when operation was performed.

MARIO A. CASTALLO.

Geschickter, Charles F., and Lewis, Dean: Pregnancy and Lactation Changes in Fibro-Adenoma of the Breast, Brit. M. J. 1: 499, 1938.

Fibroadenomas of the breast are firm, slow-growing encapsulated growths and usually give little trouble in diagnosis. However, during pregnancy and lactation they change so markedly that confusion in diagnosis often results and mutilating operations may be done unnecessarily.

A series of fibroadenomas is reported, representing every phase of pregnancy, lactation, and poor lactation involution. The changes occurring in this series are correlated with those produced experimentally in the breasts of human beings and other mammals by the injection of the various sex hormones.

The growth of mammary ducts and periductal fibrous tissue in both animals and human beings is stimulated by estrin. The histology of fibroadenomas removed at puberty, characterized by growth of ducts and stroma without evidence of lobule formation, suggests that these neoplasms represent an increased response to estrin on the part of the tissue involved. Estrin is present in increased amounts also during the first trimester of pregnancy. At this period there is a rapid growth of fibroadenomas.

Advanced fibrosis, with hyalinization or myxomatous changes in the stroma of a fibroadenoma of long standing or in tumors with an unusual intensity of estrogenic response, accounts for those fibroadenomas which remain refractory to the hormonal influences of pregnancy and lactation.

During lactation these tumors involute and often secrete, resulting in cyst formation. This change can be stimulated by the lactogenic hormone of the anterior lobe of the pituitary gland. In general, the lactogenic hormone seems to hasten and make more marked involutional changes.

F. L. ADAIR AND JOHN A. HAUGEN.

Correspondence

To the Editor:

In the February, 1939, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY Dr. E. W. Page discussed the relationship between hydatidiform moles, ischemia of the gravid uterus, and the placental origin of eclampsia. He mentioned the well-known association of moles and toxemia and from that expressed a postulation. In my own words, he reasoned that some gravid uteri cannot supply enough blood to nourish the growing products of conception; hence there comes a time when growth overcomes blood supply and ischemia occurs in the uterus and placenta. This effect in the placenta causes the production of pressor substances which are excreted into the maternal blood system by the placenta, as a mechanism to increase the maternal blood pressure which in turn increases the uterine blood supply for the placental growth. From this increased blood pressure the pre-eclampsias get their start.

This reasoning presents a fallacy which should not be left without comment. Suppose in such an individual woman the stage has just arrived when the total uterine blood supply (designated as A amount) just satisfies the growing products of gestation. The bulk of these products we will call X amount. From now on he reasons that the A blood supply will fall behind the X bulk growth. Soon bulk X will increase to bulk X plus Y with the same A amount of blood. Just where does this new bulk Y get its protein, carbohydrates, hormone, and vitamin supply to form this new mass of tissue Y? It cannot get it from the uterine supply A which can only supply the bulk X.

Basically the fallacy of this reasoning lies in the fact that the author assumes that from the time of conception the fertilized ovum has the inherent power of growth regardless of food supply. To make it sound ridiculous, let us say, cut off all the blood and lymph supply to the uterus and still the products of gestation will continue to grow.

Food supply is the basis of growth without which no tissue will grow. Hyperplasia at the expense of bulk might occur but new bulk cannot be created without new molecules supplied to it. If blood A just satisfies bulk X the products of conception will stop further growth in the sense of increased mass. In my belief, there is no reason for assuming that uterine ischemia depends upon independent placental growth.

GEORGE F. PENDLETON, M.D.

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Reply by Dr. E. W. Page

To the Editor:

Dr. Pendleton has quite properly raised the much discussed question as to the relation between growth and blood supply. Recent experiments by Drury (*J. Exper. Med.* **68:** 693, 1938) have shown that, when the blood supply to the kidney of a young rabbit is limited, that kidney will continue to grow until an equilibrium is reached and then growth is stopped. Not only will the excretory function of that kidney continue to be normal, but its "demand" for blood is greater than its supply, and it is able to effect severe hypertension through a humoral mechanism, presumably by the liberation of a pressor substance. Should the blood supply to the gravid uterus similarly be limited, the rate of growth would, as Dr. Pendleton suggests, undoubtedly be retarded and eventually stopped. It is my contention that when this equilibrium is reached the placenta, like the kidney, is capable of effecting hypertension through some humoral mechanism. Whether the placenta or fetus continues to increase in size during the acute hypertensive phase of late toxemias would obviously be very difficult to determine clinically.

Actual proof of this concept must, of course, rest in the laboratory. We have, in a series of unpublished experiments, limited the blood supply to the gravid uteri of dogs by partial constriction of the aorta below the renal vessels and have observed a gradual rise of blood pressure beginning within twenty minutes and eventually reaching a considerable height. After release of the clamp, the blood pressure will return to its basal level. This rise of blood pressure is not obtained after removal of the pregnant uterus, nor in a nonpregnant dog, and must therefore be accomplished through some humoral mechanism. This phenomenon has never been described before, and much work is needed, of course, to elucidate its mechanism. The results to date, however, are quite in accord with my theory of etiology of eclamptic hypertension.

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Items

Directory of Medical Specialists

The Advisory Board for Medical Specialties will issue in December the first edition of the Directory of Medical Specialists listing the more than 16,000 specialists certified to date by the twelve American Boards and the two affiliate Boards in the Specialties.

This Directory will have three sections. The first will be devoted to a brief discussion of the Advisory Board for Medical Specialties, its organization and objectives. The second section will have fourteen separate divisions, one for each American Board with a geographic and a detail biographic listing of its Diplomates. Each of these divisions will give full information regarding requirements for admission to examinations for certification, details of organization of each Board, and other general information. The third and final section will be a complete alphabetic list of all the 16,000 Diplomates, with their addresses and indications of specialty certification.

It is expected to issue the Directory every two years. No charge is made for any listing in the Directory, and only the names of the specialists certified by the American Boards will be included.

It represents an effort officially to inform the lay and medical public regarding the present strong movement for certification of qualified medical specialists, and is expected to have wide use as a reference work in this respect.

The Directory should be invaluable to the entire medical profession in the reference of patients, as well as in many other ways, and the individual support of this new project of the American Boards is earnestly solicited.

The Directory will be sold generally to physicians, libraries, hospitals, and others by subscription. Such subscriptions at $3.50 per copy, may be made through the Columbia Press, 2960 Broadway, New York, N. Y., or through the office of the Directing Editor, Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh, Pa.

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Candidates for reexamination in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later

than November 15, 1939.   Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II examinations must be on file in the Secretary's Office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

LAS INCRECIONES DEL OVARIO.   Par Carlos Colmeira Laforet, La Coruna. Liberia "Gali." Santiago de Compostela, Spain. 1939.

THE ENDOCRINE GLANDS. By Max A. Goldzieher, Endocrinologist, Governeur Hospital and Brooklyn Women's Hospital, New York, etc. Illustrated with 271 figures, 916 pages. D. Appleton-Century Company, New York, 1939.

PRIESTS OF LUCINA. The Story of Obstetrics. By Palmer Findley, M.D. Illustrated, 421 pages. Little, Brown & Company, Boston, 1939.

WHAT IT MEANS TO BE A DOCTOR. By Dwight Anderson. Public Relations Bureau, Medical Society of the State of New York, New York, 1939.

A HANDBOOK OF ELEMENTARY PSYCHOBIOLOGY AND PSYCHIATRY. By Edward G. Billings, M.D., Assistant Professor of Psychiatry, University of Colorado School of Medicine, etc. The Macmillan Company, New York, 1939.

STERILITY AND IMPAIRED FERTILITY. By Cedric Lane-Roberts, Gynecological Surgeon, Royal Northern Hospital; Albert Sharman, Assistant Surgeon, Royal Samarital Hospital in Glasgow; Kenneth Walker, Surgeon to Genito-Urinary Department, Royal Northern Hospital; and B. P. Wiesner, Consulting Biologist, Royal Northern Hospital. Illustrated, 419 pages. Paul B. Hoeber Inc., New York, 1939.

MATERNAL CARE AND SOME COMPLICATIONS. Edited by Dr. F. L. Adair, approved by American Committee on Maternal Welfare, Inc. University of Chicago Press, Chicago, 1939.

DIE GONORRHOEE DER FRAU. Von Dr. Karlheinz Sommer, Marinestabsarzt, Universitaets Frauenklinik in Leipzig. Mit 47 Abbildungen, 185 Seiten. Verlag von Georg Thieme, Leipzig, 1939.

WACHSTUM, GESCHLECHT UND FORTPFLANZUNG, als ganzheitliches, erbmaessig-hormonales Problem. Von Professor Dr. Ludwig Seitz. With 125 illustrations including color plates, 410 pages. Verlag von Julius Springer, Berlin, 1939.

Erratum

In the article "Studies on the Concentrations of Estrogenic and Gonadotropic Hormones in the Serum of Pregnant Women" by Dr. A. E. Rakoff in the September issue of the JOURNAL, the second paragraph of the legend under Fig. 1, page 373, beginning "In further studies in early pregnancy, etc." should appear with the legend for Fig. 2, page 374. This correction has been made in the author's reprints.